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SHORT- AND LONG-TERM RESULTS AND QUALITY OF LIFE IN OPEN INGUINAL HERNIA REPAIR

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ACADEMIC DISSERTATION

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“In order to change an existing paradigm you do not struggle to try and change the problematic model. You create a new model and make the old one obsolete.”

– R. Buckminster Fuller

ABSTRACT

AIMS: Comparison of short- and long-term outcomes from contemporary mesh implants, exploration of changes in patients' health related quality of life, and search for predictors of chronic postoperative pain in open inguinal hernia repair were the aims of this thesis.

METHODS: Among 394 patients, a prospective randomized double-blind comparison was conducted between a novel self-attaching composite mesh (Parietene ProGrip™, 40 g/m²; Covidien, Dublin, Ireland) and a sutured light-weight mesh (Parietene Light™, 38 g/m²; Covidien). Clinical assessment before and one year after operation, a symptom diary during immediate convalescence, and telephone contact were used as means of collecting outcome data.

Two- and five-year outcomes after open inguinal hernia correction either using a bilayer polypropylene mesh device (Prolene® Hernia System, 105 g/m²; Ethicon Endo-Surgery, Somerville, New Jersey, USA) or standard tension-free repair (Surgipro™, 84 g/m²; AutoSuture, Norwalk, Connecticut, USA) were collected by means of a postal questionnaire, telephone contact, and clinical assessment in 300 patients. Outcomes were analyzed and compared.

Health-related quality of life data before and 3 or 12 months after open inguinal hernia repair were gathered by means of RAND 36-Item Health Survey 1.0 (RAND Corporation, Santa Monica, California, USA) during two prospective trials from altogether 159 patients aged at least 65 years and 373 patients aged under 65 years. Quality of life data were analyzed and compared.

A database of 932 open mesh-based hernia repairs from three prospective trials with chronic pain as the primary outcome measure was formed and subjected to regression analysis for predictors of post-hernioplasty pain.

RESULTS: Complication rates, postoperative pain, pace of convalescence, chronic pain, discomfort, skin sensory function, and recurrence were equivalent between the self-attaching mesh and sutured light-weight mesh. Applying the self-attaching mesh was faster (34 min vs. 42 min, $p < 0.001$). Median sick leave was two weeks. At one year, pain while resting was perceived by 4.7% of patients, and in 2.0% pain interfered with everyday life. Discomfort was felt by 25.4% of patients, and 9.5% experienced sensation loss in the operated groin. One recurrence (0.3%) was encountered at one year.

Sensory dysfunction of groin skin was rarer 5 years after the operation with the sutureless bilayer device than with standard tension-free repair (5.0% vs. 13.9%, $p = 0.022$). Other long-term outcome between the two treatments did not differ. Occurrence of chronic pain while resting diminished over time: from 6.8% at 2 years to 1.3% at 5 years after the operation. Discomfort was reported by 25.2% of patients at 5 years. Overall recurrence rate at 5 years was 1.3%. Some 93% of the operated patients were satisfied with their operation.

Four RAND-36 dimensions showed improvement in both the older and younger patient groups after open inguinal hernia repair: pain, limitations caused by physical health problems, physical functioning, and social functioning. Complication rates between age groups did not differ.

Higher preoperative visual analogue scale (VAS) score (odds ratio, OR, 1.15, $p < 0.006$), mid-weight mesh (OR 2.28, $p = 0.012$), complications (OR 5.16, $p = 0.002$), recurrence (OR 6.76, $p = 0.005$), and younger age (OR 1.02, $p = 0.027$) increased the chances of chronic pain one year after open inguinal hernia repair. Higher VAS score after hernioplasty was predicted by higher preoperative VAS scores (regression coefficient, RC, 0.10, $p < 0.001$), heavy-weight mesh (RC 0.50, $p = 0.046$), complications (RC 0.76, $p = 0.016$), and recurrence (RC 1.49, $p = 0.001$). At one year, pain while resting was present in 6.6% of patients, and a 1.2% recurrence rate was observed among database patients.

CONCLUSIONS: Standard tension-free repair of inguinal hernia yields comparable clinical outcomes to self-fixating polypropylene / polylactic acid composite mesh in the short term and to polypropylene double-layer mesh in the long term. Attachment of a light-weight polypropylene mesh with a coat of absorbing polylactic acid microhooks or with permanent polypropylene sutures yields equivalent clinical outcomes at one year after surgery. Elderly patients display similar quality of life gains from open mesh-based inguinal hernia repair as younger patients. Greater preoperative pain, heavier meshes, complications, recurrence, and patient's younger age predict the presence of chronic post-hernioplasty pain or more intense postoperative inguinal pain. The clear majority of patients are satisfied with open hernia repair.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The following publications form the basis of this thesis:

I Pierides G, Scheinin T, Remes V, Hermunen K, Vironen J. Randomized comparison of self-fixating and sutured mesh in open inguinal hernia repair. Br J Surg 2012;99:630-636.

II Pierides G, Vironen J. A prospective randomized clinical trial comparing the Prolene Hernia System® and the Lichtenstein patch technique for inguinal hernia repair in long term: 2- and 5-year results. Am J Surg 2011;202:188-193.

III Pierides G, Mattila K, Vironen J. Quality of life change in elderly patients undergoing open inguinal hernia repair. Hernia 2013;17:729-736.

IV Pierides G, Paajanen H, Vironen J. Factors predicting chronic pain after open mesh based inguinal hernia repair. *Submitted.*

The publications are referred to in the text by their Roman numerals. The copyright holders have permitted reprinting.

ABBREVIATIONS

cPTFE	condensed polytetrafluoroethylene (polymer)
ePTFE	expanded polytetrafluoroethylene (polymer)
MRI	magnetic resonance imaging
OR	odds ratio
PCG	polyglyconate (absorbing copolymer of polyglycolic acid and trimethylene carbonate)
PDS	polydioxanone (absorbing polymer)
PET	polyethyleneterephtalate (“polyester”, polymer)
PGA	polyglycolic acid, polyglycolide (absorbing polymer)
PGCL	poliglecaprone, polyglycolic-co-caprolactone (absorbing copolymer of polyglycolic acid and caprolactone)
PGL	polyglactin (copolymer of polylactic acid and polyglygolic acid)
PHS	Prolene® Hernia System; Ethicon Endo-Surgery Inc., Somerville, New Jersey, USA (commercial bilayer mesh device)
PLA	polylactic acid, polylactide (absorbing polymer)
PP	polypropylene (polymer)
ProGrip	Parietene ProGrip®; Covidien, Dublin, Ireland (commercial mesh device)
PVDF	polyvinylidene fluoride (polymer)
QALY	quality-adjusted life-year
QoL	quality of life
RAND-36	RAND 36-Item Health Survey 1.0; RAND Corporation, Santa Monica, California, USA (health-measuring instrument, public domain)
RC	regression coefficient
RCT	randomized controlled trial
SD	standard deviation
SF-36	Short Form (36) Health Survey®; Medical Outcomes Trust, Health Assessment Lab, QualityMetric Inc., Hanover, New Hampshire and Lincoln, Rhode Island, USA (health-measuring instrument)
TEP	totally extraperitoneal (type of laparoscopic mesh placement)
TIPP	transinguinal preperitoneal (type of open mesh placement)
VAS	visual analogue scale (pain measure)

1 INTRODUCTION

Inguinal hernia has earned some of the earliest records of any medical condition, and the pursuit to treat it forged the basis of surgery (Lau 2002, Van Hee 2011). Today, the ailment has been enlisted among global priority one surgical conditions, and inguinal hernia repair is one of the most frequent surgical procedures worldwide (Bay-Nielsen et al. 2001, Mock et al. 2010).

Male lifetime risk for developing an inguinal hernia has been surveyed at 24%, while the estimated figure for women lies under 5% (Abramson et al. 1978, Javid and Brooks 2007). Prevalence increases with age. Depending on policy and resources, yearly inguinal herniorrhaphies per 100000 inhabitants range from 30 in rural sub-Saharan Africa to 275 in the USA (Rutkow 2003, Grimes et al. 2012). For years, repair of inguinal hernia has been among the 10 most common operations in the Nordic countries. A comprehensive cost analysis put the price (2007) for one open mesh-based inguinal hernia repair and its sequelae within a 5-year period at 4250€ (US$ 5500) in Northern Europe (Eklund et al. 2010a).

The etiology of adult inguinal hernia is not well understood. Anatomy or connective tissue-related vulnerability is suspected to underlie inguinal hernia formation (Hendry et al. 2008). A predisposition is likely to be congenital. Muscle and nerve function, processus vaginalis remnants, and collagen-related flaws are among the factors emerging in pathophysiological models (Abrahamson 1998).

The natural course of inguinal hernia is unclear. Indicative of an overall progressive condition is the finding that most asymptomatic groin hernias grow in size and become symptomatic over time (Mizrahi and Parker 2012). Statistics on incarceration or strangulation are scarce or indirect, and accordingly, mortality from inguinal hernia is only crudely estimable. The European Hernia Society has deemed a watchful waiting protocol in mildly symptomatic patients to be safe (Miserez et al. 2014). Efficacy of different treatments is measured in ways other than pure survival advantage.

Cauterization to induce scarring may have been utilized in ancient times, but reference to actual inguinal hernia surgery dates from the 3rd century BCE (Van Hee 2011). From the late 19th century onwards, tissue repair by darning was the standard method of surgery. Today, the tension-free repair popularized by Lichtenstein and Shulman in 1986 is the most frequently executed method of inguinal hernioplasty (Lichtenstein and Shulman 1986, Rutkow 2003, Amid 2004, Reuben and Neumayer 2006). Technically easy to learn, requiring low initial expenditure, and suitable for light anesthesia forms, this technique has expanded the feasibility of hernia correction. A myriad of modifications of the tension-free concept has ensued in terms of implant material, morphology, configuration, and means of attachment as well as implant placement route and site. Recurrence now lies at approximately 2%, and this has been comprehensively shown to be generally lower than for earlier tissue plasties (Amato et al. 2012). Accordingly, research around inguinal hernia repair has shifted towards reducing adverse outcomes other than recurrence.

The most frequent setback in open mesh-based inguinal hernia surgery is now chronic post-hernioplasty pain, with a prevalence of 10-15% (Nienhuijs et al. 2007, de Goede et al. 2013). Complications, discomfort, sensation of foreign body, skin sensory disorders, urogenital pain, and sexual dysfunction are other disadvantages affecting quality of life. Reasons for chronic pain are poorly understood, but a multifactorial etiology is suspected. Patient characteristics, operation technique, implant properties, and attachment regimes are being investigated in this context. Commercial developments to produce appliances leading to better outcomes have been rapid and alluring.

Looking at today's diversified field of inguinal hernia surgery, a few key areas for clinical research emerge. Prospective and blinded studies are needed to assess new implants and attachment methods for their true clinical performance. Over a year's follow-up times in this context are rare. Health-related quality of life (QoL) is an underused measure of success in hernia surgery. Especially in the elderly, this variable could affect decision rationale. Determining which factors in today's practices are associated with chronic post-hernioplasty pain will enable sophistication of future inguinal hernia surgery. Individual tailoring of hernia treatment will be facilitated by improved knowledge about patient-related factors that predict chronic pain. This thesis explores these areas of contemporary inguinal hernia surgery.

2 REVIEW OF THE LITERATURE

2.1 INGUINAL HERNIA AS A MEDICAL CONDITION

Herniation in the groin takes place in the myopectineal orifice (H. Fruchaud) depicted in Figure 1. This is a thin area in the lower abdominal wall with a muscle-aponeurotic and bony frame covered mainly by the transverse fascia and the peritoneum. Here, connective tissue balances between elasticity for locomotion and accommodation of conduits and firmness to seal off contents of the abdominal cavity. An inguinal hernia forms above the inguinal ligament. A medial (direct) hernia protrudes medially from the lower epigastric vessels at the conjoint tendon, while a lateral (indirect) hernia centers on a conduit – the spermatic cord or the round ligament. The classification by Nyhus is the most widely known (Holzheimer 2005). According to the Swedish Hernia Register 56% of inguinal hernias are lateral, 36% medial, and 8% combined (Nordin 2014).

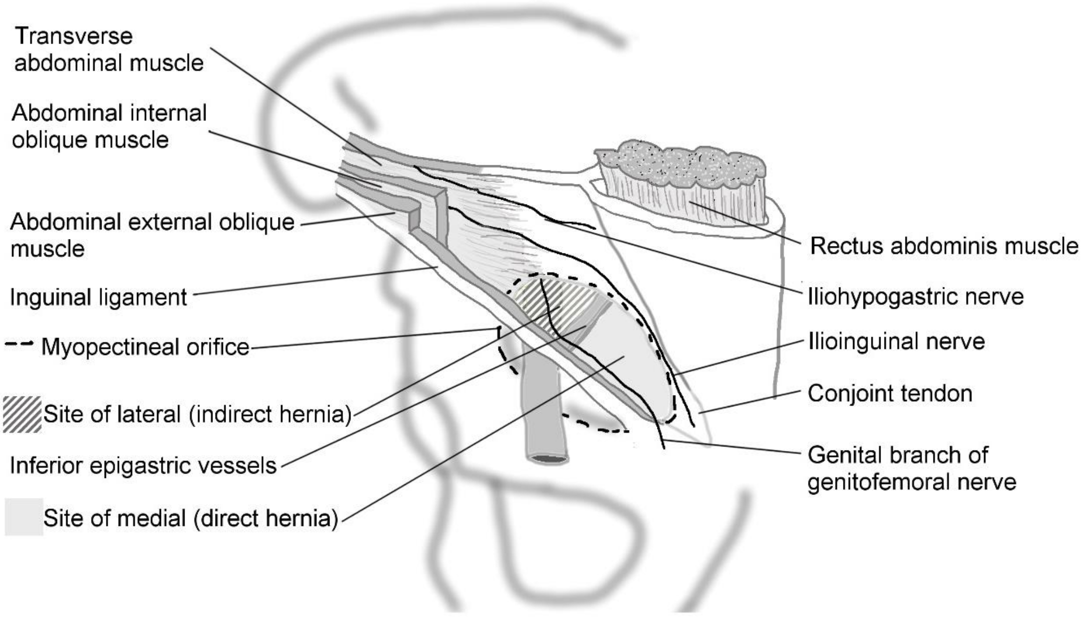


Figure 1. *Anatomy relevant to inguinal hernia.*

Development of inguinal hernia in adulthood is thought to require predisposing structural elements. Raised abdominal pressure can normally be fended against at the myopectineal orifice by active and passive mechanisms. On the other hand, there is recent indication that lateral hernias are associated with occupational exposure to lifting and prolonged walking (Vad et al. 2012). Evolutionary and embryological transitions have been considered roots of human susceptibility to inguinal hernia. Bipedal stature puts the myopectineal orifice under more strain than quadrupedal stature; the gravitational force is directed caudally on a vulnerably directed inguinal canal, which is housed by an elongated and thinned groin (Abrahamson 1998). Medial and lateral hernias may bear etiological dissimilarity. A patent processus vaginalis or its remnants increase the chances of developing a lateral hernia, but does not necessarily lead to one, as demonstrated by adult autopsies (van Veen et al. 2007a). Insufficiency of contractibility at the internal ring – likened to a sphincter – has been deemed a reason for lateral hernia (Macgregor 1945). Another distortable shutter mechanism at the conjoined tendon produced by the downward movement of the oblique internal muscle was suggested by computer simulation (Fortuny et al. 2009). A systematic review of studies on positive family history support inheritance in inguinal hernia, although the patterns and exact targets remain unknown (Burcharth et al. 2013).

Speculation of pathological groin tissue as the culprit for inguinal hernia has expanded into suspicion of a systemic connective tissue disorder centering on collagen-related flaws (Keith 1924, McVay et al. 1967, Wagh et al. 1974, Read 2004). Genetics of connective tissue affect the firmness of the transverse fascia. Accordingly, increased rates of inguinal hernia are found in people with, for instance, defective fibrillin (Marfan's syndrome), collagen (Ehlers-Danlos syndrome, osteogenesis imperfecta), transforming growth factor beta receptor 1 or 2 (Loeys-Dietz syndrome), elastin (Williams syndrome), and angiotensin-converting enzyme genes (Antoniou et al. 2013). Support provided by collagen, the most common protein in the extracellular matrix, is affected by its density, the proportions of different types, the fiber cross-linkage patterns, and the molecular structure. Evidence for and against decreased cross-linkage of collagen fibers in association with medial hernias have been found (Wagh and Read 1972, Pans et al. 2001). There is indication for a decrease in the collagen type I/III ratio in inguinal hernia patients compared with hernia free controls (Klinge et al. 1999b, Casanova et al. 2009). Comparison of skin or rectus sheath collagen and elastin densities among hernia patients and controls have yielded contrasting results (Friedman et al. 1993, Ozdogan et al. 2006). A balance of proteinase-antiproteinase activity affects collagen deposits. Increased collagen protease activity in the blood samples of inguinal hernia patients relative to healthy controls was first noted among smokers and later also among non-smokers (Cannon and Read 1981, Smigielski et al. 2011). The same matrix metalloproteinases were found to be overexpressed in the transverse fascia of patients with inguinal hernia relative to those without (Bellon et al. 2001, Aren et al. 2011).

Inguinal hernia patients display pathology at the histological level. Biopsies from the borders of the inguinal hernia opening have revealed inflammatory cells, muscular atrophy, fibrohyaline degeneration, and myocyte fatty dystrophy as well as degeneration of nervous tissue not present in hernia-free cadavers. In vitro activity of fibroblasts and myocytes harvested from the hernia sac and the surroundings was lower in inguinal hernia patients than in controls (Ajabnoor et al. 1992). On the other hand, a process of tissue remodellation in the face of inguinal breakage has been suggested (Pans et al. 2001). Both association and no association between inguinal hernia and abdominal aortic aneurysm has been found (Antoniou et al. 2011, Henriksen et al. 2013). Recently, a connection between inguinal hernia and thoracic aortic disease was reported (Olsson et al. 2014). Summarizing, inheritable properties of connective tissue seem to play a role in the emergence of adult inguinal hernia.

What to expect as the natural course of adult inguinal hernia is not well established. This is partly due to prompt surgical correction having been the norm for decades. Evidence of an overall progressive condition exists. Groin pain and irreducibility increase with patient-reported duration of inguinal hernia; these reach 90% and 30%, respectively, at 10 years (Hair et al. 2001). A considerable number of followed asymptomatic patients will cross over to surgery because of pain and an increase in hernia size (Mizrahi and Parker 2012, Fitzgibbons et al. 2013). Apart from pain, there is a general disease burden associated with inguinal hernia. Health-related QoL, especially physical dimensions, is impaired in inguinal hernia patients in comparison with the general population as demonstrated by SF-36® (Lawrence et al. 1997). Some indication exists that QoL is inversely dependent on hernia size (Mathur et al. 2006). A study on 309 males revealed that preoperatively 36% did not experience any pain and 30% had a pain visual analogue scale (VAS) score of 3.0 or under from their inguinal hernia during physical activity (Magnusson et al. 2014). Totally symptom-free were 25% of the men, while the rest experienced pressure, burning, tension, or gurgles due to the hernia. However, if only referred patients are investigated, the natural course of a significant volume of hernias in unreferred patients is neglected.

An inguinal hernia is capable of precipitating the serious medical emergencies of incarceration and strangulation. Two randomized prospective trials yielded a risk of inguinal incarceration per hernia-year of 0.2 and 0.8, while a records-based study established a risk of 0.4 (Neutra et al. 1981, Fitzgibbons et al. 2006, O'Dwyer et al. 2006). Detailed risk profiling according to hernia size, rate of expansion, intra-abdominal pressure, or other patient characteristics analogically to, for instance, aorta aneurysm does not exist. The strategy of watchful waiting in minimally symptomatic male patients may prompt more detailed understanding of outcome probabilities. Retrospective analysis from the United Kingdom revealed that a policy change towards watchful waiting was associated with both an increase in emergency inguinal hernia operations and mortality (Hwang et al. 2014). This is not unexpected as a 7-fold mortality from emergency operations as opposed to elective repair of inguinal hernia was determined in the Swedish Hernia Register (Nilsson et al. 2007). Limited knowledge regarding the natural course of inguinal hernia leads to inaccurate morbidity and lethality estimates, and therefore treatment recommendations are based on other rationale.

Epidemiological information about inguinal hernia is mostly indirect. A few field sampling surveys exist. Clinical examinations conducted in 1969-1971 in western Jerusalem among men from 25 countries revealed a prevalence of 24% with an age-related increase: 15% among 25-34-year-olds and 40%

among 65-74-year-olds (Abramson et al. 1978). A 2011 sampling in Uganda carried out among randomly selected males determined a 9.4% prevalence of inguinal hernia (Löfgren et al. 2014). Some 2.4% of 18-34-year-olds had inguinal hernia, whereas 37% of men over 55 years had one. Examination of Turkish conscripts aged 20-22 years in 1995 revealed a 3.2% prevalence of inguinal hernia (Akin et al. 1997). The cumulative risk for hospitalization due to inguinal hernia based on interviews and medical records in the USA during 1982-1993 for individuals aged 25-74 years was 14% (Ruhl and Everhart 2007). It increased from 7% at 24-39 years to 23% at 60-74 years. In the United Kingdom, Sweden, and Taiwan, 1.3 to 1.8 new inguinal hernia diagnoses per 1000 inhabitants are made yearly with males comprising approximately 90% of these (Primatesta and Goldacre 1996, Nilsson et al. 1997, Liu et al. 2014). Globally, over 20 million inguinal hernia repairs are performed annually (Bay-Nielsen et al. 2001). Of known surgical conditions, inguinal hernia is one of the most common. Because of the large volumes, even the smallest improvements in inguinal hernia surgery translate into marked health and economic gains.

2.2 PROSTHETIC REPAIR

An era of tissue rearrangement to close the hernia defect was initiated by Eduardo Bassini in 1887 (Bassini 1887). Solutions for challenging inguinal hernia cases included the additional use of autologous fascia transplants, metallic gauzes, and in 1944 a sheet of polyamide (Aquaviva and Bounet 1944). Use of a polyethylene preperitoneal "insert" in inguinal hernia repair was reported in 1948, and a polypropylene mesh was introduced in 1959 (Thompson 1948, Usher and Gannon 1959). Routine application of a mesh prosthesis alone was, however, popularized by Lichtenstein and Shulman as part of "tension-free repair", which has become the prevailing way of inguinal hernia correction worldwide (Lichtenstein 1970, Lichtenstein and Shulman 1986, Reuben and Neumayer 2006, Eklund et al. 2010a).

The advantage of prosthetic surgery over tissue repair in terms of recurrence has been comprehensively attested; the rate drops by 50-75%, and the difference appears to grow over time (Scott et al. 2001, Bisgaard et al. 2007). Influenced by cohort size, response rate, follow-up time, and specialist input, prospective trials with a follow-up of 5-10 years have reported a recurrence rate ranging from 0.1% to 8% for the Lichtenstein repair and 20% for tissue plasties (Amid et al. 1996, Hernández-Granados et al. 2000, van Veen et al. 2007b, Nienhuijs and Rosman 2014, Droeser et al. 2014). The current reoperation rate for recurrence after prosthetization regardless of facility specialist status or time from primary surgery is approximately 2% in Scandinavian databases (Wara et al. 2005, Nordin 2014).

The concept refined by Lichtenstein and his team included, in modern terminology, open anterior placement of a heavy-weight monofilament polypropylene mesh attached to the inguinal ligament and the internal oblique aponeurosis and muscle with a continuous polypropylene suture under local anesthesia as a day-case. Originally, however, prostheses were inserted posteriorly as an augmentation to tissue repair. Later, this evolved into the transinguinal preperitoneal approach (TIPP) (Nyhus et al. 1959, Schumpelick and Arlt 1996). Here, a space is created in the preperitoneal fat deep to the transverse fascia by blunt dissection and a mesh is spread to lie posteriorly against the muscle layer. A higher abdominal pressure serves theoretically to push the implant against the abdominal wall, creating hold. Later, avoidance of nerve damage due to the posterior plane of dissection has been advocated. Devices with posterior components, including the bilayer Prolene® Hernia System (PHS, Ethicon Endo-Surgery Inc., Somerville, New Jersey, USA), are among the myriad of adjustments to the tension-free repair (Gilbert et al. 1999).

2.3 IMPLANTS

A mesh reinforces the abdominal wall by its own tensile properties and by inducing scarring. Both are affected by implant characteristics. Surgical trauma and scar tissue alone seem not to address the disease sufficiently, as indicated by frequent medial recurrences after applying completely absorbable meshes (Symeonidis et al. 2013, Negro et al. 2013, Ruiz-Jasbon et al. 2014). Tensile requirements to resist distension at the myopectineal orifice depend theoretically on intra-abdominal pressure, diameter of pressure site (representing area), and wall thickness (Laplace's law). An intra-abdominal pressure maximum of 20 kPa, yielding a tensile requirement of 16 N/cm, and the prospect of less stiffness led to the proposal of more slender prostheses (Klinge et al. 1998). Newer considerations set tensile requirements somewhat higher. A maximum mean pressure of 23 kPa in the abdominal cavity of healthy young people was measured in a small cohort (Cobb et al. 2005). Taking into account an intra-abdominal pressure of 30 kPa in the obese, a tensile stress requirement of 50 N/cm was calculated. Most contemporary PP, PET and PTFE meshes meet this requirement in biaxial burst testing, with the exception of a few ultralight meshes, but scarring increases tensile strength in vivo (Deeken et al. 2014). The original meshes with more polymer are now considered "standard" or "heavy-weight" (> 80-90 g/m^2), while more slender meshes are called "mid-weight" or "light-weight". Cut-off points between these categories vary. Although the unit is actually for weight distribution (g/m^2), the term "weight" is used in communication.

Polypropylene (PP) is the most utilized and researched implant material in hernia surgery, followed by polyethylene terephthalate (PET, "polyester") and expanded polytetrafluoroethylene (ePTFE). These polymers are relatively easy to synthesize, are made in high commercial volumes, possess good tensile strength, and are non-toxic. Polyvinylidene fluoride (PVDF) and condensed PTFE (cPTFE) are examples of newer mesh materials. What clinical effects implant materials and architecture may entail has been asked from the onset of tension-free repair, and these questions have even found judicial manifestations in the USA. For example, surface chemistry, yarn structure, knit configuration, pore size, material distribution, mesh shape, and material combinations have been studied for recurrence, infection, shrinkage, isotropy, elasticity, integration, adhesion potential, wear, ease of application, costs, patient comfort, and chronic pain. The level of detail at which implants are studied or characterized often surpasses knowledge about the biomechanics, biochemistry, and pathophysiology of the abdominal wall. Devices containing separate portions of PP, PET, and ePTFE theoretically allow comparison of how the polymers fare in a fixed human environment. Contrasted with the pristine mesh, such explanted devices subjected to chemical analysis and electron microscopy revealed the following: PP surface cracks at weave junctions, gets oxylated and carbonylated, and loses overall weight, PET shows fraying but less weight loss, and ePTFE stays intact in electron microscopy but displays cross-linkage or oxidation and experiences weight loss (Cozad et al. 2010). Contemporary mesh materials are therefore not completely inert in the human body. Clinical success of a mesh device is thought to be ultimately determined by its short- and long-term biocompatibility. That is, how well a foreign structure agrees with the living environment and performs its designated tasks.

2.4 FOREIGN BODY REACTION

Chemical and physical properties of an implant affect how the body reacts to it. Factors such as hydrophobicity, charge, roughness, and rigidity of the surface as well as nanotopography, pore size, and tortuosity (pore twisting) determine connective tissue behavior with respect to a scaffold (Hsin-I Chang and Wang 2011). At implantation, numerous events take place at the tissue-prosthesis interface. Proteins are triggered, altered, and drawn on foreign material depending on its surface chemistry. Generally, more hydrophobic surfaces attract more kinds of proteins. Inflammation via coagulation, the complement system, and antibodies activates defensive and repair cells. Protein adsorbance influences cell adhesion. The nature and extent of the exposed surface area affects the course of the foreign body reaction. Indicative of this, while other properties were kept constant, silicone implants with a reduced surface area induced weaker foreign body reactions in the rat brain (Skousen et al. 2011). Furthermore, the extent of surface area of PP particles as well as coating them with either anionic, cationic, hydrophobic, or hydrophilic functional groups affected inflammation, cellular infiltration, and fibrosis in mice (Kamath et al. 2008).

Intensity, duration, and the cellular profile during the proliferation phase affect the outcome of healing. In the “granuloma” around a mesh fiber, overlap in numerous cell types was observed, indicating a complex histological response (Klinge et al. 2014). Cells involved comprise macrophages, mast cells, monocytes, polymorphonuclear leucocytes, fibroblasts, and their derivatives in proportions affected by the characteristics of the foreign body. Part of the action of these cells is to try and destroy alien elements using enzymes and oxidants. Indissoluble material is isolated under scar tissue. Fibroblasts adhere best to less hydrophobic and more positively charged surfaces and prefer certain nanotopography, while adsorption of e.g. serum albumin prevents their adhesion (Tamada and Ikada 1993, Schneider et al. 2004, Dalby 2005, Wei et al. 2009). In vitro, human skin fibroblast loading followed hydrophilic surface chemistry and total surface area. It was strongest in multifilament PET (2000 µm pores), followed by multifilament polylactide (PLA) / polyglyconate (PCG) (1500 µm pores), light-weight monofilament PP (2000 µm pores, 170 µm fiber thickness), and lastly monofilament heavy-weight PP mesh (440 µm pores, 110 µm fiber thickness) (Gao et al. 2014).

Animal models and explantation from patients indicate that the foreign body reaction generated by current mesh devices stabilizes at approximately 3 months, but a low-intensity reaction continues indefinitely. A resolved tissue response is consistent with fibrosis, the extent of which is mainly affected by the number, activity, and time span of macrophage-stimulated fibroblasts (Luttikhuizen et al. 2006). The speed and pattern of fibrosis have been postulated to affect clinical mesh performance.

2.5 FEATURES AFFECTING MESH BIOCOMPATIBILITY

The interaction between a scaffold and host tissue is complex, and isolating single mesh characteristics for closer examination is challenging. Reduction of the amount of polymer in a mesh has been evaluated to yield clinically beneficial outcomes, and today’s meshes are classified according to their weight distribution (g/m^2). This refers to a textile’s physical characteristics. From the point of view of biocompatibility, simple weight distribution may not be the most relevant aspect. For the inflammation phase of the foreign body reaction, a more significant variable may be the gross surface area (m^2) produced by all polymer fibers exposed to the living environment. Fiber density, thickness, and yarn filament count determine the gross surface area as well as the weight distribution. Histological follow-up of 225 rats for up to 90 days showed that inflammation, fibrosis, and tissue stiffness was highest for the PP mesh having the largest gross surface area (m^2) relative to the other PP mesh types (Klosterhalfen et al. 1998). This did not go hand in hand with mesh weight distribution (g/m^2). Thicker encapsulation was observed for increasing fiber diameter in PET and polylactide (PLA) implants (Sanders et al. 2002). That fiber surface area rather than the amount of polymer is responsible for this is indicated by the core of a single fiber not appearing to participate in the foreign body reaction in the short term. Electron microscopy during the first 3 months after implantation reveals no biological material inside individual PET fibers. Furthermore, effective early exchange of molecules between the interior and the exterior of a PET fiber seems unlikely due to the very low permeability of the polymer in physiological conditions.

On the other hand, pore size rather than surface area was interpreted as the determinant for the tissue response in rats (Klinge et al. 2002b). Here, an absorbable component (polyglactin, PGL) in one of the compared meshes may have interfered with the results. Indicative of interference, a similar light-weight double-filament PP / PGL mesh displayed prolonged high levels of foreign body reaction and increased collagen deposition in comparison to monofilament PP meshes with small pores in a rat model (Pereira-Lucena et al. 2014). However, there is also evidence that intensity of tissue response is affected by the structure and amount of polyglactin as well as the local conditions (Klinge et al. 1999a).

Comparing tissue response between particular polymers seems equally prone to interference. In rats, at 90 days after implantation, multifilament PET exhibited the highest amounts of inflammatory cells and cytokines, followed by monofilament light-weight PP, monofilament PET, and monofilament knit PTFE (Nguyen et al. 2012). Here, the multifilament and monofilament PET meshes had comparable pore sizes, but the former contained more polymer and had a larger gross surface area. The hydrophobic PTFE typically shows the mildest foreign body reactions, which may result from increased protein adsorption. ePTFE structures cause less adhesions on the peritoneal side than PP structures, as the former also induces less cellular colonization and angiogenesis (Bellon et al. 1995). More hydrophilic polymers tend to induce a stronger foreign body reaction.

Porosity is another focus in mesh morphological research. Currently, “pore size” may refer to any level of mesh architecture ranging from nanotopography via micrometric porosity to loop “megapores” in the millimeter range. Interstices inside double-filament or multifilament threads are often left without clear categorization. New nomenclature suggests “effective porosity” for histologically beneficial pores, whereas “textile porosity” would describe the technical structure (Muhl et al. 2008). Initially, the call for “macroporosity” was derived from canine models showing that porosity had an effect on how capable inflammatory cells, fibroblasts, and capillaries were at occupying foreign material (White et al. 1981, Bobyn et al. 1982). A threshold of beneficial macroporosity was set at 75 µm in an effort to classify mesh materials, while pores under 10 µm were deemed impenetrable for the macrophage and granulocyte (Amid 1997). Today, the latter pore size is thought to be a threshold for any tissue ingrowth and pore sizes span up to 4000 µm. Pore size appears to affect foreign body reaction, mesh shrinkage, and distribution of fibrosis along the mesh. In a canine model, 90 days after implantation of 3 PP meshes with different pore sizes, lymphocyte count, foreign body granuloma width around threads, and shrinkage were lowest for the largest pored mesh (Jerabek et al. 2014). In tighter meshes with threads in close proximity, fibrosis merges into a solid continuum through the entire foreign body, whereas in looser organized meshes loop centers remain fibrosis-free, yielding an intermittent scar. This has an impact on the elasticity of the abdominal wall. Thresholds for "scar bridging" may be polymer- and environment-dependent; for PP, an interfilament distance under 1000 μm leads to bridging (Conze et al. 2008). A revival of mesh categorization primarily according to porosity has been suggested backed by ranking of numerous explanted mesh devices for beneficial histology (Klinge and Klosterhalfen 2012).

The feature combinations of newer meshes may provide more insight into what influences a hernia device's biocompatibility. cPTFE has been condensed to a solid membrane where macroscopic pores are etched during mesh manufacturing (expanded PTFE has an internal microporous structure). Non-woven PP is a light-weight felt-like latticework of PP microfibrils. A cPTFE mesh with a pore size of 2400 μm prompted higher collagen deposits, required a higher pull-out force, and shrank less than an ePTFE mesh (pore size 25-100μm), while both displayed similar cellular proliferation in a rat model (Voskerician et al. 2007). Another study with swine showed the least intestinal adhesions, tissue incorporation, fibrosis, and cell proliferation for ePTFE, followed by cPTFE, non-woven PP, and heavy-weight PP, with ePTFE also shrinking the most (Raptis et al. 2011). A non-woven light-weight PP mesh recruited more macrophages and induced heavier superficial fibrosis, while a heavy-weight PP mesh recruited less macrophages and caused less but penetrative fibrosis in rats (Weyhe et al. 2006). The absorbable components of composite meshes have been utilized to make handling of slender meshes easier and to provide means of attachment. Absorbable components influence the foreign body reaction, thus warranting attention. By careful selection of materials and architectural features, foreign body reaction and fibrosis can potentially be influenced. Table 1 gives an overview of reported relative findings in this respect.

Dimension changes in explanted PP meshes used in inguinal hernia repair were noted early. Suspicions of this circa 20% shrinkage being a source of discomfort, pain, and recurrence were accordingly raised and updates concerning size, positioning, and securing of the mesh in tension-free repair issued. Contraction of PP and PET meshes of up 65% and 25%, respectively, has been observed in the anterior position in animal models. Knit monofilament PTFE mesh shrank the most, followed by light-weight PP mesh and multifilament PET mesh in rats (Asarias et al. 2011). Mechanisms of contraction are poorly understood. Already soon after implantation, a mesh seeks a new stance. This was attested by magnetic resonance imaging (MRI) of an iron-coated PVDF mesh that showed considerable wrinkling within 2 days of both open and laparoscopic inguinal hernia repair (Hansen et al. 2013). Wrinkling may lead to focally intensified tissue responses. MRI imaging in a rabbit model indicates that most of the mesh contraction (circa 20%) takes place before tissue ingrowth in heavy-weight PP, light-weight composite PP / poliglecaprone (PGCL), and PVDF meshes (Endo et al. 2014). If the foreign body reaction is mild and slow, the mesh is able to contract more. Accordingly, an inverse relationship between extent of tissue integration and shrinkage was observed in a porcine model for PP and PET meshes, with also wider meshes shrinking less (Gonzalez et al. 2005). Certain surface chemistry may be capable of promoting macrophages, and therefore, early fibrosis, which secures the mesh swiftly into position and allows less shrinkage. Indicative of this, fluoropolymer-coated monofilament PET displayed earlier macrophage recruitment, earlier and higher fibrosis, higher biaxial burst strength, and less shrinkage than monofilament heavy-weight PP, which provoked more polymorphonuclear cells in a porcine model (Marois et al. 2000).

The complex concept of biocompatibility requires that a mesh be considered primarily from a biochemical perspective and in nanoscale and microscale spatial dimensions. There is indication that an implant's surface chemistry and the extent of its total area influences protein disruption and coverage, and therefore intensity and course of inflammation, which, in turn, influences cell adherence and proliferation. Porosity, on the other hand, may affect cell migration and patterns of collagen deposition. Devices that are able to induce suitable inflammation with their surface chemistry, to provoke a rapid proliferative phase favoring macrophages and fibroblasts, to aid in cell migration, and to yield appropriately shaped fibrosis seem to contract less and produce sufficient tensile strength without excessive abdominal wall stiffness. This, in all likelihood, translates into good clinical performance, i.e. low recurrence and little discomfort and chronic pain.

Table 1. *Rough overview of reported relative characteristics and effects of mesh materials in vitro, in animal models, or after explantation. 1 = highest, 4 = lowest.*

Effect	Heavy-weight PP	Light-weight PP	Multifilament PET	Knit ePTFE
Hydrophobicity	2	2	3	1
Inflammation	1	3	2	4
Fibroblast loading	3	2	1	
Fibrosis	2	2	1	3
Shrinkage	3 or 2	2	4	1

(Rosch et al. 2003, Gonzalez et al. 2005, Jacob et al. 2012, Zogbi et al. 2013, Gao et al. 2014, Wood et al. 2013)

2.6 COMPLICATIONS OF HERNIA SURGERY

Mesh colonization by bacteria is subject to similar adhesion and migration related laws as tissue ingrowth. In vitro, rougher (more hydrophilic) PP filaments were colonized more by Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus (Coughlin et al. 1999). On the other hand, E. coli and S. aureus adhered best to multifilament PET, followed by monofilament PTFE and monofilament PP (Gungor et al. 2010). The most influential mesh feature favoring Staphylococcus epidermidis and S. aureus adherence to various monofilament and multifilament PP, ePTFE, cPTFE, and PET meshes was available surface area (Sanders et al. 2013). However, elevated bacterial adhesion does not necessarily signify susceptibility to clinical infection. This is exemplified by PP, whose multifilament structure accommodated significantly more S. aureus in vitro than its monofilament form, but the contaminated mesh did not cause more infections in rats (Klinge et al. 2002a). Mesh structures not permitting penetrance of macrophages and granulocytes are thought to be a risk for infection. True late-onset infection in open inguinal hernia mesh surgery is rare and difficult to verify; a medical records-based study provided a yearly incidence of 0.02 (Delikoukos et al. 2007). Theoretically, a better mesh biocompatibility allows the host tissue to launch a more efficient immunological response against microbes.

Short-term complications observed in inguinal hernia surgery seem to scatter according to the operation technique. The Swedish Hernia Registry recorded between 1998 and 2009 a 7.8% 30-day complication rate and a 0.1% 30-day mortality in open anterior mesh inguinal hernia surgery comprising 3.5% hematoma, 1.4% surgical infection, 0.8% severe pain, 0.6% urinary retention, 1.8% other complications, and a reoperation rate of 0.5% (Lundstrom et al. 2012). The 30-day complication rate was lower for open anterior mesh repair than for plug, open preperitoneal, and laparoscopic techniques. Overall, complication rates were higher for general and regional anesthesia, patients at least 65 years of age, long surgery time, and acute operation. Repetition produced by the largest volumes may be responsible for the relative safety of open anterior surgery. Whether elective inguinal hernia repair harbors more risks for elderly people was investigated retrospectively; equal complication rates for ASA III and IV patients relative to healthier individuals were found if the repair was performed under local anesthesia (Sanjay et al. 2006). Supporting this, a prospective comparison (n = 160) concerning Lichtenstein repair under local anesthesia in under 56-year-olds and at least 80-year-olds (Goldman cardiac risk III excluded) found no differences between the groups for 30-day complications or mortality (Palumbo et al. 2014). In view of short-term complications, Lichtenstein's approach appears to offer an overall good standard technique across all patients.

Long-term complications after open inguinal hernioplasty other than infection, pain, discomfort, and recurrence are mostly urogenital: genital or coital pain, ischemic orchitis, and testicular atrophy. Suspicions of inflicted infertility in males have not been confirmed. Contrasting national records on infertility treatments with the Swedish Hernia Register revealed no association (Hallen et al. 2012). Urogenital complications have been viewed to result from changes in testicular blood flow, nerve damage, mesh or scar interference, effects from the foreign body reaction, and immunological responses. Tangible harm seems rare. Larger prospective studies (n = 590-2906) with clinically obtained outcomes have reported an incidence of 0-1.4%

for testicular atrophy at 1-3 years after Lichtenstein repair, with no difference between heavy-weight and light-weight PP mesh (Kark et al. 1998, Bringman et al. 2006).

The epidemiology of urogenital pain and sexual impairment from inguinal hernia or its repair is inconclusive. A large questionnaire study based on the Danish Hernia Database revealed a 9.8% prevalence of moderate to severe pain during sexual activity, leading to 2.8% pain-induced moderate to severe sexual dysfunction 1.5 years after inguinal hernia repair, with no differences between operation types (Aasvang et al. 2006). Similarly, an 11% prevalence of testicular pain 3 years after Lichtenstein repair with a heavy-weight mesh was reported (Paajanen and Varjo 2010). Without preoperative values and because complaints, rather than satisfaction, are more readily self-reported, these figures may be an over-estimation. A large prospective randomized controlled study (RCT) determined a 3% prevalence of testicular pain before inguinal hernia operation (Eker et al. 2012). Another prospective study with a 5–year clinical follow-up measured rates of 0.7% for testicular pain and 1.1% for pain during sexual activity after Lichtenstein repair with a heavy-weight PP mesh (Eklund et al. 2010b). One prospective study revealed 5.8% new sexual dysfunctions 3 months after plug and patch repair, but these resolved over time (Zieren et al. 2005).

Testicular blood flow and antisperm antibodies have been scrutinized in a few studies. A double-filament PP mesh (105-8 g/m^2, pore size 1000-1600 μm) placed either laparoscopically with titanium tacks or openly with PGL sutures led to no change in testicular blood flow or serum antisperm antibodies 4-5 months after operation compared with before operation in complication-free patients (Stula et al. 2014). However, ultrasonographically visible testicular ischemia causing pain in the early period did lead to increased antisperm concentrations in the late period. In the early period, intratesticular perfusion was diminished after laparoscopy relative to preoperative values. Open surgery led to a decrease in fewer blood flow parameters. The reason for this transient change in perfusion remains obscure. Edema has been proposed, while another reason may be the pneumoperitoneum.

2.7 CHRONIC POST-HERNIOPLASTY PAIN

The tension-free repair has not reduced chronic operation site pain after inguinal hernia correction (Bay-Nielsen et al. 2004, van Veen et al. 2007b). Chronic pain is a persisting unpleasant sensory and emotional experience, with 3 months being the most convenient boundary to acute pain according to the International Association for the Study of Pain. Current criteria for persisting post-surgery pain comprise development of pain after surgery, pain duration of at least 2 months, and no other explanation for the pain (Macrae and Davies 1999). Recently suggested updates include expansion of the duration to 3-6 months and a pain location that matches surgery (Werner and

Kongsgaard 2014). The suggestion of a longer duration of pain is suitable for prosthesis surgery, as resolution of the foreign body reaction takes time.

Considering the diversity in ways and time-points for collecting pain data and the difficulty in objectifying pain, it is no wonder that there is marked variation in the reported rates of chronic pain after inguinal hernia surgery. Precision and harmonization in pain measurement in hernia research has been called for (Kehlet et al. 2002). Reports of chronic pain after open mesh repair range from 0 to 36% at 3-82 months, yielding a pooled prevalence of 11-12%, approximately one-third of which is substantial enough to interfere with everyday life (Aasvang and Kehlet 2005, Nienhuijs et al. 2007). However, if a stricter definition of chronic post-surgery pain is applied, these figures may be substantially lower. A study assessing groin pain before and after open inguinal hernia surgery revealed that the rate of newly established inguinal pain after repair was, in fact, only 1.6% (Magnusson et al. 2014). Furthermore, this did not have a relative effect on postoperative health-related QoL.

There is evidence both for and against patient psychology having an influence on chronic pain after inguinal hernia repair. One study (n = 90) compared a number of psychological measures before hernioplasty and pain 4 months after the procedure; lower scores in optimism (Life Orientation Test, 2-item version) were associated with more pain (Worst Pain Intensity) (Powell et al. 2012). Another study (n = 442) found no correlation between preoperative psychometrics (Pain Catastrophizing Scale, Hospital and Depression Scale) and pain-related impairment (Activity Assessment Scale) at 6 months (Aasvang et al. 2010b). A patient's responsiveness to sensory stimuli appears to play a role; higher preoperative sensitivity to heat stimuli prospectively predicted postoperative chronic pain in inguinal hernia patients (Aasvang et al. 2010b). This sensory responsiveness seems to ultimately have a genetic foundation. The elderly displayed a reduced perception of heat stimuli, giving a potential explanation for why older people have less chronic post-hernioplasty pain.

Lesions to nerve fibers through surgical trauma, the implant, the foreign body reaction, or nerve entrapment in sutures, folds, or scar tissue have been suggested as a possible source of chronic post-hernioplasty pain. At 6 months after hernia repair, disturbances of thermal sensing signifying actual nerve damage correlated with the existence of chronic pain (Aasvang et al. 2010b). Disturbed sensory function was more often found in patients undergoing open rather than laparoscopic inguinal hernia repair, indicating that an anterior surgical route or the anterior position of the mesh may increase the risk of nerve lesions. That laparoscopy results in less chronic pain in the first years relative to open mesh placement is backed by the results of a meta-analysis (McCormack et al. 2009). A more diffuse triggering of nociceptors by inflammation, tension, or scar tissue has also been proposed as a reason for persistent pain. It appears that chronic post-hernioplasty pain is of both neuropathic and nociceptive origin in varying proportions combined with central nervous plasticity (Aasvang et al. 2010a).

The role of individual nerves in the development of chronic pain has been studied in a few trials. A large prospective study (n = 973 hernias) on open mesh hernioplasty found that at 6 months the occurrence of pain was associated with what happened to the three susceptible nerves in the operation field; pain was more common and stronger if nerves had been intentionally divided or not identified than if nerves had been identified and spared (Alfieri et al. 2006). However, in another prospective comparison (n = 244), both respect and disregard of the iliohypogastric, ilioinguinal, and genitofemoral nerves yielded equivalent pain at 6 months (Bischoff et al. 2012). Similarly, a meta-analysis of open inguinal mesh hernioplasty found that even though at 6 and 12 months hypesthesia was present more often, there was no difference in rates of chronic pain in patients in whom the ilioinguinal nerve was routinely divided compared with patients in whom it was spared (Hsu et al. 2012). All in all, the causes of pain and particularly the role of individual nerves in its etiology are inconclusive.

2.8 PROSTHETIZATION AND PAIN

The relationship between specific implant features and chronic pain has been investigated mostly up to one year after open inguinal hernia surgery. Comparison between pure PP and PET meshes is rare. One study (n = 78) found no differences at 3 months in disturbing pain, patient complaints, physical performance, or recurrence between a heavy-weight PP and a large-pore multifilament PET mesh (79 g/m^2) after open inguinal surgery (Sadowski et al. 2011). Reduction of implanted material seems to yield benefits in terms of chronic pain without more recurrence. Meta-analysis of RCTs on open hernioplasty indicated less chronic pain and sense of foreign body after repair with light-weight PP meshes (pure and composite) compared with heavy-weight PP meshes, while recurrence was unaffected (Smietanski et al. 2012, Zhong et al. 2013). The same result was obtained for laparoscopy (Sajid et al. 2013b).

Investigation into the effect of pore size on chronic post-hernioplasty pain has been sporadic. At 6 months after open surgery (n = 134) with either a monofilament PP / PGCL mesh (3000-4000 µm pores) or a monofilament PP mesh (1000 µm pores), the same pain, foreign body sensation, QoL, and skin sensory function were found (Nikkolo et al. 2014a). However, the absorbing component in one of the meshes may have influenced the results. Concerning absorbable components, a meta-analysis of open surgery found that a double-filament PP / PGL mesh with 4000 µm pores (32 g/m^2 after absorption) was associated with less sensation of foreign body, while chronic pain and recurrence were the same compared with monofilament heavy-weight PP meshes (Gao et al. 2010). The prolonged tissue reaction from absorbable components seen in animal models may decrease benefits from material reduction. Evaluation of non-flat meshes typically yield results equivalent to those of flat anterior meshes in terms of pain and recurrence. Plug and patch types or the PHS yielded no differences in chronic pain or recurrence in comparison with anterior sutured meshes within the first years after operation in two meta-analyses (Li et al. 2012, Sanjay et al. 2012).

Whether various mesh fixation methods lead to differing pain outcomes in line with hypotheses on nerve entrapment or irritation has been tested increasingly. Fixation with glue yielded less chronic pain without a difference in numbness or recurrence relative to permanent or absorbable sutures in meta-analysis of RCTs spanning 3 months to 5 years after open surgery (Colvin et al. 2013). Smaller meta-analyses of glue versus sutures (permanent, mid-term, and slow absorbing) found either less pain for the glue group at 3-6 months but no difference at 12 months or no differences at all (de Goede et al. 2013, Ladwa et al. 2013). Meta-analysis also revealed less chronic pain from glues than from titanium staples for laparoscopy (Shah et al. 2014). Penetrative fixation therefore seems to be associated with more chronic pain than superficial adhesives. A meta-analysis of RCTs on sutureless TIPP versus anterior sutured mesh repair found a reduction in chronic pain for the former at 3-96 months with recurrence remaining the same (Sajid et al. 2013a).

Combined, the above implies that an increased chance of severing nerves mechanically either during anterior dissection or by penetrative attachment regimes may be associated with more post-hernioplasty pain. On the other hand, a meta-analysis of RCTs yielded no difference in chronic pain, discomfort, or recurrence between an openly placed light-weight PP mesh attaching with a layer of absorbing PLA microhooks (ProGrip®) and a sutured light-weight PP mesh at 3-46 months (Fang et al. 2014). Therefore, there appears to be dissimilarity in how different types of non-invasive mesh fixation methods perform relative to chronic pain. If and how PLA might counterbalance the benefits of non-penetrative fixation should be tested further. This is a second case where beneficial features are possibly neutralized by an absorbing mesh component.

Statistical predictive models are able to provide relative risks from perioperative variables of today's inguinal hernia repairs for a particular outcome. Regression analysis requires large cohorts acquired typically from surveys or databases rather than single prospective trials. This affects expressive power. Recent analyses suggests that sex does not independently affect the chance for post-hernioplasty pain, while the body mass index (BMI), facility specialist status, and hernia type have produced contrasting results. Younger age, higher level of recalled pain before surgery, anterior dissection, open surgery, postoperative complications, operating on recurrent hernia, shorter follow-up time, and use of heavy-weight mesh have been identified as risk factors for chronic post-hernioplasty pain (Franneby et al. 2006, Massaron et al. 2007, Nienhuijs et al. 2007, Kalliomaki et al. 2008). The risk of chronic pain was the same between Lichtenstein and mesh plug repair as well as between Lichtenstein and PHS repair in another study (Zhao et al. 2009). More prospective research or registries with outcome data are needed to establish implant features with the least risk for persistent pain and patient characteristics indicative of an increased risk for pain.

2.9 LONG-TERM OUTCOMES

Obtaining late follow-up data prospectively in medical research is challenging, and the field of inguinal hernia is no exception. Passing time increases the probability of both non-response and complaint reporting, which leads to decreased statistical strength and skewed results. Simultaneously, rising life expectancy and active seniority stretch performance requirements of hernia repairs and materials. A few dozen RCTs on open mesh-based inguinal hernia surgery span currently over 5 years, while the 10-year mark is surpassed only exceptionally (Bhangu et al. 2014). Questionnaires by post or telephone may yield more data through lesser effort from all parties involved, but physical examination is more accurate. Comparison of ways to detect hernia outcomes showed a 94-98% predictive value for patients' self-reported denial of hernia recurrence, while approximately 10% of recurrence was missed through a combination of questionnaires and selective clinical examination (Kald and Nilsson 1991, Vos et al. 1998, Haapaniemi and Nilsson 2002). Validation also revealed that approximately 15% of reported "groin pain" had a source other than the operation site on physical examination. Table 2 displays some of the largest prospective series spanning at least 5 years.

Long-term data seem to portray an outcome profile differing somewhat from short-term results. Generally, recurrence increases, while the rates of severe pain and hypesthesia decline over time. Rates of chronic pain after different interventions display a tendency to equalize with time, but more numbness seems to remain after open anterior surgery. Clinical follow-up (n = 1275, down from 1370) showed that moderate to severe chronic pain after open anterior placement of a monofilament PP mesh (92 g/m^2, pore size 800 µm) decreased over time and reached the figures for totally extraperitoneal (TEP) repair at 5 years (3%), while recurrence was comparable (2%) (Eklund et al. 2009, Eklund et al. 2010b). Similarly, a median of 7.3 years after operation (n = 154, down from 168), clinical visits showed that a heavy-weight PP mesh placed in the Lichtenstein manner led to a higher rate of impaired groin sensibility than TEP (32% vs. 12%), while recurrence (3%) and chronic pain (11%) were the same (Hallen et al. 2008). On the other hand, one study (n = 482, down from 640) with PP meshes showed more chronic pain (28% versus 15%) and sensibility disorders (22% vs 1%) for the Lichtenstein repair than for TEP, while recurrence (6%) was equivalent as determined by clinical visits taking place at a median of 5 years after operation (Eker et al. 2012).

Table 2. *Late outcome of elective open mesh-based inguinal hernia surgery in selected studies.*

Mesh	Attachment	Follow-up / years	Original n / response rate	Means of follow-up	Chronic pain / moderate + severe pain	Hypesthesia / Numbness	Recurrence	Reference
Heavy-weight PP	PP suture	5	101-705 / 74-89%	Clinical	19-28% / 2-3.5%	22%	1.2%-8.1%	(Eklund et al. 2009, Eklund et al. 2010b, Eker et al. 2012, Smietanski et al. 2011)
Heavy-weight PP	PP suture	7.3	86 / 94%	Clinical	14% / 2%	32%	5.1%	(Hallen et al. 2008)
Heavy-weight PP	PP suture	10	146 / 50%	Clinical	14% / 0%	19%	0%	(van Veen et al. 2007b)
Heavy-weight PP	PGA suture	10	281 / 88%	Postal + selective clinical	24% / 0%	Not reported	2%	(Paajanen and Varjo 2010)
Double-layer (PHS®)	PP and PGL	5.5	187 / 84%	Clinical	Not reported / 1.8%	4.4%	2.3%	(Faraj et al. 2010)
Light-weight double-filament PP / PGL (Vypro II®)	PDS suture	5	133 / 64%	Clinical	12% / 0%	13%	6%	(Kim-Fuchs et al. 2012)
	N-butyl-cyanoacrylate (Histoacryl®)	5	131 / 53%		4% / 0%	13%	11%	
Light-weight non-woven PP	PP suture	5	101 / 91%	Clinical	Not reported / 2%	Not reported	1%	(Smietanski et al. 2011)
Heavy-weight PP	PP suture	5	177 / 91%	Telephone + selective clinical	Not reported / 3%	Not reported	0.6%	(Bury et al. 2012)
Light-weight monofilament PP / PGCL (Ultrapro®)			215 / 91%		Not reported / 3%	Not reported	2%	
Heavy-weight PP	PP suture	5	110 / 81%	Postal + selective clinical	25% / 6%	13%	5.6%	(Nienhuijs and Rosman 2014)
Double-layer (PHS®)	Absorbable suture		111 / 81%		21% / 7%	12%	3.3%	
Plug & patch (PerFix®)	Absorbable suture		113 / 76%		24%/ 6%	14%	9.9%	

The differences in outcomes between heavy-weight and light-weight meshes seem to become less apparent in late follow-up as well. One study (n = 356, down from 392) based on phone contact and selective clinical assessment at a median of 5 years found a chronic pain rate of 3% and a recurrence of 2%, and no difference between a heavy-weight PP and a composite light-weight PP / PGCL mesh (Bury et al. 2012). Also, a median of 5 years after open operation (n = 182, down from 202), a heavy-weight monofilament PP and a light-weight non-woven PP mesh displayed the same rate of chronic pain (2%) and recurrence (2%) as observed in clinical visits (Smietanski et al. 2011). Recurrence after using absorbing attachment seems somewhat higher than the typical recurrence rates for standard Lichtenstein repair with permanent sutures. Five years after open anterior fixation (n = 155, down from 264) of a light-weight multifilament PP / PGL mesh with either cyanoacrylate glue or polydiaxone (PDS) sutures, 8% recurrence, 8% chronic pain, and 13% hypesthesia were encountered on clinical examination, with no difference between groups (Kim-Fuchs et al. 2012). The impact of time to clinical results stresses importance of obtaining good quality late outcomes.

2.10 QUALITY OF LIFE AND RETURN OF INVESTMENT

QoL instruments offer a standard and comprehensive way of determining and comparing impact from inguinal hernia surgery. They are being increasingly utilized for this purpose. One use of health-related QoL data is to identify patients who benefit from hernia repair in a resource-limited setting. At 12 months after elective open anterior inguinal hernioplasty (n = 309), three SF-36® physical scores increased relative to the preoperative state in males aged 18-75 years (Magnusson et al. 2014). An increase in QoL mostly occurred in patients experiencing preoperative inguinal pain, but was also observed in patients with no pain. Another study (n = 123) revealed an increase in the SF-36® dimensions of pain, physical function, and vitality after open plug and patch surgery at 3 months (Zieren et al. 2003). The observation of QoL benefits from open inguinal hernia surgery includes the elderly population, often viewed as low-demand patients. Even a minimally symptomatic inguinal hernia (n = 40) diminished the health-related QoL in at least 75-year-old patients, and QoL was increased with open hernioplasty with a heavy-weight mesh, whereas refraining from the operation brought no change in QoL (Patti et al. 2014). This is consistent with an overall disease burden associated with the condition going beyond pain and age. The disease burden can generally be successfully lifted through open mesh-based inguinal hernia repair. Studies thoroughly comparing QoL differences after particular types of surgical interventions, implanted materials, or attachment methods are still scarce.

QoL data are also being increasingly incorporated into models for measuring the overall societal and economic impact from inguinal hernia and its treatment strategies. Results are location-bound and thus inconsistent. Return of investment (ROI) up to one year was analyzed in a prospective study (n = 225) concerning the Lichtenstein procedure with a light-weight mesh in Sweden (Palmqvist et al. 2013). For every 1€ invested, 4.5€ were returned (2011) when hospital expenses and costs from sick leave were contrasted with tariffed quality-adjusted life-years (QALY) determined via changes in pain (VAS), QoL (SF-36®), and self-rated health (EQ-5D™). Higher net ROI was obtained for more symptomatic patients. Another study on inguinal hernia in an American setting, taking into account complications, recurrence and loss of industrial productivity determined the cost / QALY for laparoscopy at $4086, for open mesh at $4290, and for open tissue plasty at $6200 in 2002 (Stylopoulos et al. 2003). It also found that facility cost and recurrence rate are the heaviest determinants of cost / QALY in inguinal hernia surgery. However, most of the efficiency and expense models rely on operation statistics spanning under 3 years. Here too, longer term analysis is required.

Fusion of evidence is being used to issue recommendations for inguinal hernia treatment from the point of view of clinical success and cost efficiency. Treatment guidelines and effectiveness analysis for adult inguinal hernia have been prepared by, for instance, the European Hernia Society, the British Hernia Society, the Society for Surgery of the Alimentary Tract, and by the Agency for Healthcare Research and Quality (under the US Department of Health). To date, no universally accepted treatment algorithm has emerged due to insufficient data.

3 AIMS OF THE STUDY

The aims of this thesis were to investigate outcomes of contemporary prosthetization, quality of life change and factors behind chronic pain associated with the surgical correction of adult inguinal hernia. Specific aims were as follows:

1. To compare the performance of a self-attaching or a double-layer mesh with standard tension-free repair in the short term or the long term.

2. To evaluate whether permanent sutures or absorbable fixation affect outcome.

3. To determine whether elderly patients benefit from inguinal hernia repair in terms of health-related quality of life.

4. To identify predictive factors for chronic post-hernioplasty pain.

4 PATIENTS AND METHODS

In Studies I, II, and III, data were collected prospectively. Study IV was a registry study in which data had accumulated from three clinical trials.

4.1 PATIENTS

Table 3 displays patient numbers and trial details of the studies. The patients were at least 16 years old, were referred, and scheduled for inguinal hernia repair as a day-case, which is the standard scheme in all of the participating hospitals. Patients not meeting the medical requirements for outpatient treatment were excluded. Local ethics committees approved the trials. All patients gave written informed consent prior to participation.

Study I patients were enrolled in two Helsinki University Hospital ambulatory surgery units (Jorvi Hospital in Espoo and Surgical Hospital in Helsinki). Patients had unilateral primary hernia.

Study II patients were enrolled in one Helsinki University Hospital ambulatory unit (Jorvi Hospital). Patients had unilateral of bilateral primary or recurrent hernia.

Study III patients were enrolled in one Helsinki University Hospital ambulatory surgery unit (Jorvi Hospital). Participants had unilateral or bilateral primary or recurrent hernia. Additionally, QoL data from patients in Study I were used in Study III.

Study IV database operations were carried out at Helsinki University Hospital (Study I patients) and at the central hospitals of Päijät-Häme (Lahti), Mikkeli, and North Karelia (Joensuu) during altogether three inguinal hernia trials. The first trial included only patients with unilateral primary hernia, while the second trial also included patients with bilateral hernia, and the third additionally patients with recurrent hernia.

4.2 RANDOMIZATION

Simple randomization by opaque sealed shuffled envelopes opened during or just prior to the operation in sequence was performed in all prospective studies. A block randomization per facility had been carried out similarly in the multicenter trial whose patients were included in the database for Study IV.

Table 3. *Patient numbers and trial details in Studies I-IV.*

Study	Period	Group	n	Age / years	Sexes F/M	BMI* / kg/m²	Hernia U/B/R %†	Anesthesia L/R/G %‡
I	2008-2010	Self-fixating	198	55 (20-79)	10/188	25 (18-36)	100/0/0	63/34/3
		Lichtenstein	196	53 (19-80)	14/182	25 (18-33)	100/0/0	61/34/5
II	2001-2004	Prolene® Hernia System	150	46 (19-72)	10/140	25 (17-36)	87/13/3	29/44/27
		Lichtenstein	150	47 (20-70)	8/142	25 (19-36)	91/9/3	44/35/21
III	2006-2008	≥65-year-olds	89	72 (65-86)	10/79	25 (17-32)	97/3/7	96/2/2
		<65-year-olds	43	48 (20-64)	3/40	25 (19-32)	91/9/5	88/5/7
IV	2003-2010	Registry	924	55 (17-88)	70/854	25 (16-41)	99/1/1	84/14/2

Values are median (range), count, or percentage
*BMI = Body mass index
†U = Unilateral, B = Bilateral, R = Recurrent
‡L = Local anesthesia, R = Regional anesthesia, G = General anesthesia

4.3 METHODS

The operations were performed by senior surgeons with good competence in open inguinal hernia surgery and sporadically by supervised surgical residents. Incision of the skin and establishment of the anterior space between the external oblique aponeurosis and the muscle layer were done similarly in all operations. Large lateral hernia sacs were divided and small lateral and large medial sacs were inverted using absorbable suture. In men, a slit for the spermatic chord was cut in the onlay patch. The iliohypogastric, ilioinguinal, and genitofemoral nerves were identified and preserved when possible and divided if damaged. The oblique aponeurosis and the skin were closed with absorbable and non-absorbable sutures, respectively. Procedures in the Lichtenstein-groups were completed according to Lichtenstein and Shulman (Lichtenstein et al. 1989).

The VAS used was a 10.0-cm-long printed line with the ends representing "no pain" and "the most intense pain imaginable". The patient drew a mark on the line denoting the current pain intensity. The distance from 0 to the patient's mark was determined with a ruler to record a numerical equivalent in cm to the first decimal place. Health-related QoL was measured with the RAND 36-Item Health Survey 1.0 (RAND-36; RAND Corporation, Santa Monica, California, USA) residing in the public domain. This is a 36-question instrument yielding 8 life quality dimensions correlating almost identically to the Short Form (36) Health Survey (SF-36®; Medical Outcomes Trust, Health Assessment Lab, QualityMetric Incorporated, Hanover, New Hampshire and Lincoln, Rhode Island, USA) (Hays et al. 1993). The dimensions are physical functioning, limitations caused by physical health problems (role / physical), pain, social functioning, emotional well-being, limitations caused by emotional problems (role / emotional), energy, and general health. The RAND-36 instrument has been translated and validated for the Finnish population (Aalto et al. 1999).

STUDY I Between 2008 and 2010 in 394 patients either a self-fixating PP / PLA mesh (Parietene Progrip™, 80 g/m², 40 g/m² non-absorbable PP, pore size 1600 x 1000 µm; Covidien, Dublin, Ireland) was placed anteriorly or a standard Lichtenstein operation was performed using a light-weight monofilament PP mesh (Parietene Light™, 38 g/m2; pore size 1500×1700 µm; Covidien) attached with 2/0 PP sutures (Prolene®; Ethicon, Somerville, New Jersey, USA). The novel implant has PLA microhooks to one side of a light-weight monofilament precut PP mesh and attaches on tissue like a burr. It was pressed into position with enough spread over the pubic tubercle and the inguinal ligament, and its opening for the spermatic chord was adjusted (Chastan 2006). Preoperatively, the patients filled in the RAND-36 questionnaire and inguinal pain scores in VAS for lying, during coughing, and when moving. After the operation, patients kept a symptom diary for 2 weeks marking their daily VAS scores. A telephone inquiry concerning convalescence and need for sick leave was made at 2 weeks by a blinded examiner. One year after the operation, the patients filled in a second RAND-36 questionnaire and were clinically assessed by a blinded examiner. The primary endpoint of the study was chronic pain at one year.

STUDY II From 2001 to 2004 among 300 patients either a bilayer mesh made of monofilament PP (Prolene® Hernia System, 105 g/m², pore size ~500 µm; Ethicon) was inserted or a standard Lichtenstein operation was performed using a monofilament PP mesh (Surgipro™, 84 g/m², pore size 260 µm; AutoSuture, Norwalk, Connecticut, USA) and PP sutures (Vironen et al. 2006). The bilayer device is made of Prolene® (Ethicon) mesh: it has a flat underlay part that is inserted in the preperitoneal fat to lie against the muscle layer, a cylindrical connector in the middle, and an overlay patch that comes to lie anteriorly (Gilbert et al. 1999). A posterior space for the PHS was created by blunt dissection. In 13% of the patients having a large direct hernia, the onlay part was secured medially with 2-3 PGL sutures (Vicryl®; Ethicon). At 2 and 5 years, the patients were sent a questionnaire to identify recurrence and to inquire about pain, changes in testicle size, discomfort, and skin sensory function and were offered a clinical evaluation. Symptomatic patients and those who so wished were telephoned. Patients who scheduled an appointment, who suffered from marked symptoms, or in whom a recurrence was suspected were clinically assessed.

STUDY III During 2006 to 2008 an elective open mesh-based inguinal hernia repair was performed on 89 patients aged at least 65 years and on 42 patients aged under 65 years (Mattila et al. 2011). The patients filled in the

RAND-36 questionnaire before their operation and 3 months after the procedure. QoL change within an age group and differences between age groups were analyzed along with QoL data from Study I. Additionally, predictors for change of QoL were searched among the following patient and operation related variables: age, sex, preoperative VAS score during movement, BMI, type of hernia, and mesh type.

STUDY IV A database of 932 open inguinal hernia operations (924 patients, 8 with bilateral hernias) was formed. It included A) the operations from Study I, B) from 2003 to 2004 performed 232 operations with one of three meshes: a monofilament PP mesh (Premilene®, 82 g/m², pore size 800 µm or Premilene LP®, 55 g/m², pore size 750 µm; B. Braun, Melsungen, Germany) or a double-filament PP / PGL mesh (Vypro II®, 82 g/m², 32 g/m² non-absorbable PP, pore size 3000-4000 µm; Ethicon) (Paajanen 2007), and C) between 2007 and 2009 performed 306 operations using a monofilament PP mesh (Optilene®, 60 g/m², pore size 1500 µm; B. Braun) attached either by glue (Glubran®; GEM, Viareggio, Italy) or 3/0 PGA suture (Dexon®; United States Surgical, Norwalk, Connecticut, USA) (Paajanen et al. 2011). The database included a determination of chronic pain at one year after surgery and a measurement of VAS before and 1-4 years after surgery. Other database variables were hernia type (lateral, medial, combined, recurrent), surgical complication (nerve damage, infection, bleeding, hematoma, combinations), mesh type (heavy-weight, mid-weight, light-weight), anesthesia type (local, regional, general), duration of operation, time to follow-up, one-year recurrence, patient's age, sex, and BMI.

The following were taken to denote the presence of chronic pain at one year: complaint of bothersome pain in the operation site, reporting the regular need for pain medication due to inguinal pain, and reporting pain while resting or a measurement of VAS > 3.0 while resting. This VAS threshold was based on the concept of analgesic success and suggested cut-off points between mild and moderate pain (Mantha et al. 1993, Hawker et al. 2011, Loos et al. 2008). Division into light-weight (35-50 g/m²), mid-weight (50–80 g/m²), and heavy-weight (>80 g/m²) mesh categories followed previous suggestions (Bellon 2009).

4.4 STATISTICAL METHODS

Statistics were analyzed using IBM SPSS Statistics 18.0-22.0® (IBM, Armonk, New York, USA) and STATA® (StataCorp LP, College Station, Texas, USA). An α of 0.05 (two-tailed) was taken to express statistical significance. In designing Study I, a chronic pain and discomfort rate of 26% after Lichtenstein repair was anticipated as indicated by previous studies. A rate of 50 % less was assumed for the self-fixating mesh. Detection of this at a 90% power required two groups of 190 patients. Categorical variables were subjected to Fisher's exact and Pearson's χ^2 tests. Continuous variables in unrelated samples were tested with Mann-Whitney-U test and in related samples with Wilcoxon matched-pairs signed-rank test. Repeated measures ANOVA was applied to continuous repeatedly measured variables. RAND-36 scores were tested against Finnish population norms utilizing the independent samples Student's t test (Walters 2004). In Study III, patient and operation-related variables were modeled in bootstrapped-type multivariate regression analysis to identify those that independently predicted RAND-36 change. The Half-scale rule was applied to missing QoL data according to RAND-36 and SF-36® instructions. In Study IV, logistic regression analysis among patient- and operation-related variables was carried out to identify those that independently predicted presence of chronic pain at one year. Additionally, the variables in Study IV were subjected to a linear regression model to determine which of them were independently associated with higher postoperative VAS scores.

5 RESULTS

5.1 NOVEL SELF-ATTACHING MESH IN THE SHORT TERM

Comparison of outcomes between the self-fixating composite mesh and Lichtenstein procedure with light-weight mesh is presented in Tables 4 and 5 and Figure 2 (Study I). Patients' attendance at the one-year follow-up was 90.9%. The only statistically significant difference between the two treatments was duration of operation, which was a median of 8 minutes shorter for the self-attaching mesh.

Table 4. *Comparison of outcomes between the self-fixating composite mesh and the Lichtenstein procedure during primary convalescence (Study I).*

Outcome	Self-fixating (n = 198)	Lichtenstein (n = 196)	*p-value**
Complication			
Hematoma	1 (0.5)	1 (0.5)	0.999
Infection	1 (0.5)	3 (1.5)	0.371
Prolonged pain	0	1 (0.5)	0.497
Bleeding	1 (0.5)	0	0.999
Aspiration	0	1 (0.5)	0.999
Division of a nerve	3 (1.5)	0	0.623
Duration of operation / min	34 (20-74)	42 (24-88)	**<.001†**
Sick leave / day	13 (6-33)	13 (1-79)	0.658

*Fisher's exact test, except †Mann-Whitney *U* test
Values are count (percentage) or median (range)

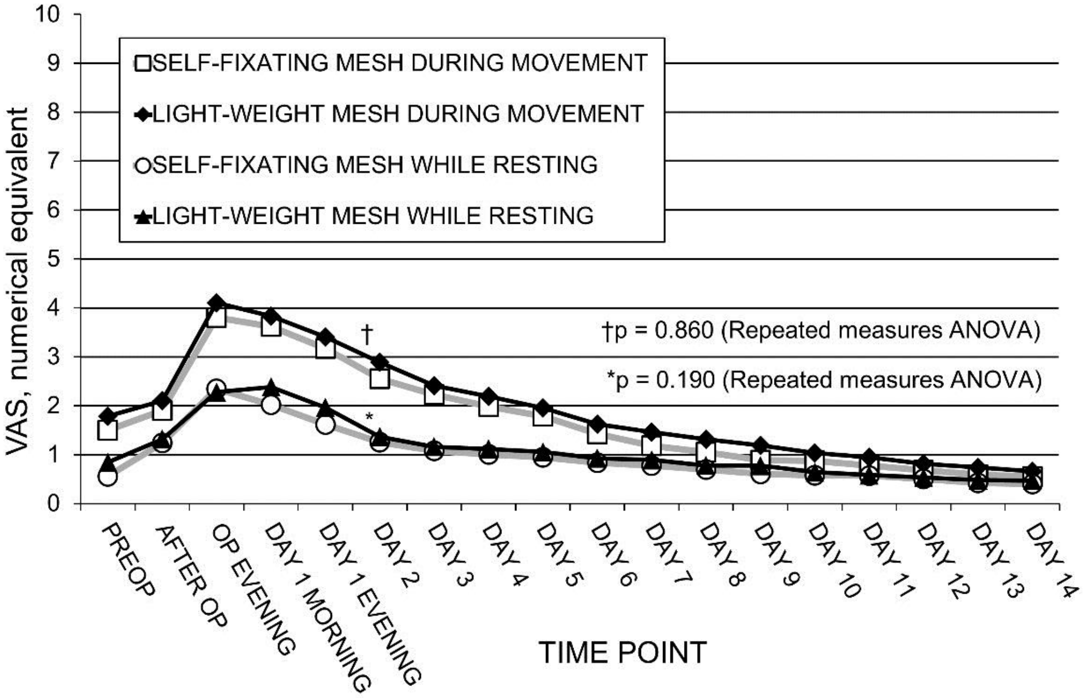


Figure 2. *Mean groin pain in VAS numerical equivalent after open placement of self-fixating mesh or Lichtenstein procedure during primary convalescence (Study I).*

Table 5. *Comparison of one-year outcomes between the self-fixating mesh and Lichtenstein procedure (Study I).*

Outcome	Self-fixating (n = 179)	Lichtenstein (n = 179)	*p-value**
Chronic pain or discomfort	65 (36.3)	61 (34.1)	0.658
Discomfort other than pain	49 (27.4)	42 (23.5)	0.395
Pain			
while resting	11 (6.1)	6 (3.4)	0.214
when coughing	7 (3.9)	5 (2.8)	0.557
during movement	25 (14.0)	24 (13.4)	0.878
interferes with everyday life	2 (1.1)	8 (4.5)	0.448†
Pain medication needed	2 (1.1)	8 (4.5)	0.104†
Mesh perceptible	17 (9.5)	16 (8.9)	0.855
Sensory disturbance	21 (11.7)	17 (9.5)	0.493
Scrotal swelling	3 (1.7)	0	0.248†
Recurrence	0	1 (0.6)	0.999

*Pearson's χ^2 test, except †Fisher's exact test
Values are count (percentage)

5.2 BILAYER MESH IN THE LONG TERM

Comparison of inguinal hernia repair using the PHS with performing standard Lichtenstein procedure yielded the late outcomes displayed in Tables 6 and 7 (Study II). The five-year attendance was 77.6%. Diminished skin sensory function at 5 years after the operation was significantly rarer after the operation with the PHS; this was the only difference found between the two patient groups.

Table 6. *Comparison of two-year outcomes between repair with the PHS (Prolene® Hernia System) and standard Lichtenstein procedure (Study II).*

Outcome	PHS n = 114	Lichtenstein n = 121	Total n = 235	*p-value**
Satisfaction	107 (93.0)	111 (92.5)	218 (92.7)	0.955
No anomalous sensations	54 (47.4)	54 (45.0)	108 (46.2)	0.716
Pain				
when moving	18 (15.8)	17 (14.2)	35 (15.0)	0.728
while resting	7 (6.1)	9 (7.5)	16 (6.8)	0.680
Sensation of tension	22 (19.3)	33 (27.5)	55 (23.5)	0.139

* Pearson χ^2 –test (two-tailed)
Values are count (percentage)

5.3 QUALITY OF LIFE CHANGE

Table 8 shows postoperative complications among patients in Study III. No differences in short-term complications were found between patients aged 65 years and over and patients aged under 65 years. Figures 3, 4, and 5 exhibit RAND-36 comparisons after open mesh-based inguinal hernia repair. The preoperative scores for physical function, limitations caused by physical health problems, and pain were lower or the same among male inguinal hernia patients compared with their counterparts from the Finnish general population. Postoperatively, the scores were higher among male patients than

Table 7. *Comparison of five-year outcomes between repair with the PHS and standard Lichtenstein procedure (Study II).*

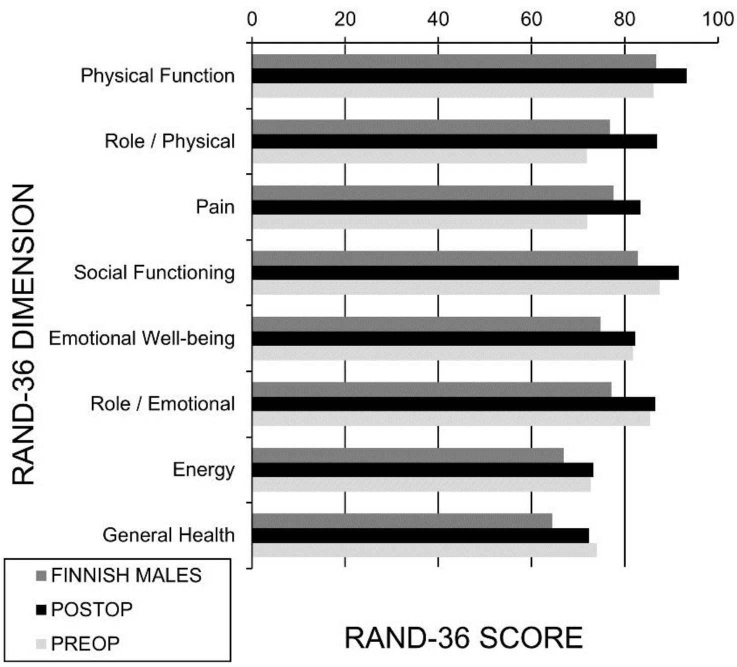
Outcome	PHS n = 122	Lichtenstein n = 110	Total n = 232	*p-value**
Mesh noticeable	16 (13.7)	18 (17.1)	34 (15.3)	0.474
Pain				
while resting	1 (0.8)	2 (1.8)	3 (1.3)	0.605
when coughing	2 (1.6)	1 (0.9)	3 (1.3)	0.999
standing up	4 (3.3)	5 (4.5)	9 (3.9)	0.739
during movement	9 (7.4)	13 (11.8)	22 (9.5)	0.249
interferes with everyday life	2 (1.9)	2 (2.1)	4 (2.0)	0.999
medication needed	1 (0.9)	2 (2.0)	3 (1.4)	0.603
Abnormal skin sensation	6 (5.0)	15 (13.9)	21 (9.3)	**0.022**
Abnormal skin sensation, no pain	4 (3.7)	11 (11.8)	15 (7.5)	**0.034**
Discomfort	23 (20.4)	32 (30.5)	55 (25.2)	0.086
Cumulative recurrence	1 (0.8)	2 (1.8)	3 (1.3)	0.620

*Pearson χ^2 –test or Fisher's exact test
Values are count (percentage)

Table 8. *Short-term complications in Study III patients.*

Complication	≥65 years (n = 89)	<65 years (n = 45)	*p-value**
Bleeding	2	0	0.550
Hematoma	4	1	0.663
Infection	0	2	0.110
Nausea	2	2	0.602
Diarrhea	1	0	0.999
Headache	0	1	0.999
Voiding problem	2	0	0.550

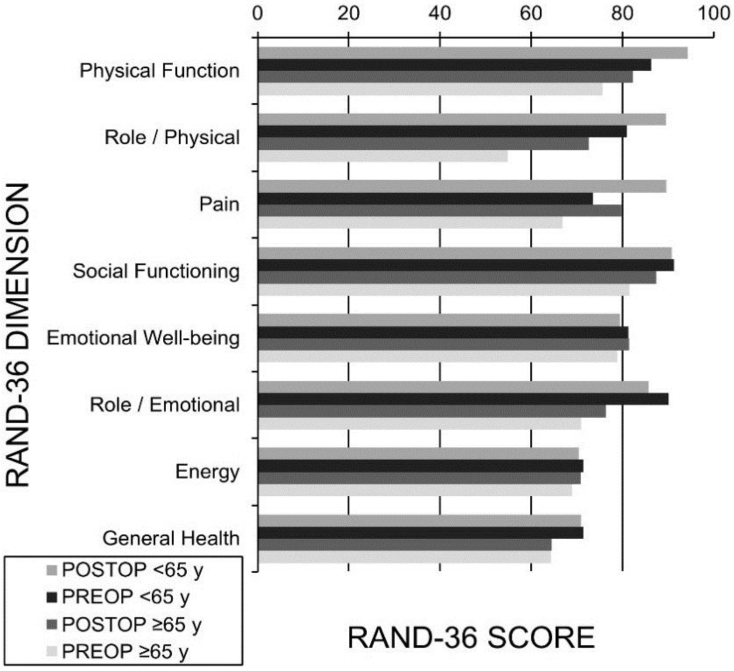
*Fisher's exact test



*p** Preop males vs. Finnish males	*p** Postop males vs. Finnish males	*p*† Preop males vs. postop males (n=329)
0.751 ‡	<0.001	**<0.001**
0.01 ‡	<0.001	**<0.001**
<0.001 ‡	<0.001	**<0.001**
<0.001	<0.001	**<0.001**
<0.001	<0.001	0.246
<0.001	<0.001	0.739
<0.001	<0.001	0.384
<0.001	<0.001	0.059

*Student's t test.
†Wilcoxon signed-rank test.
Sample score > population score, except ‡sample score ≤ population score.

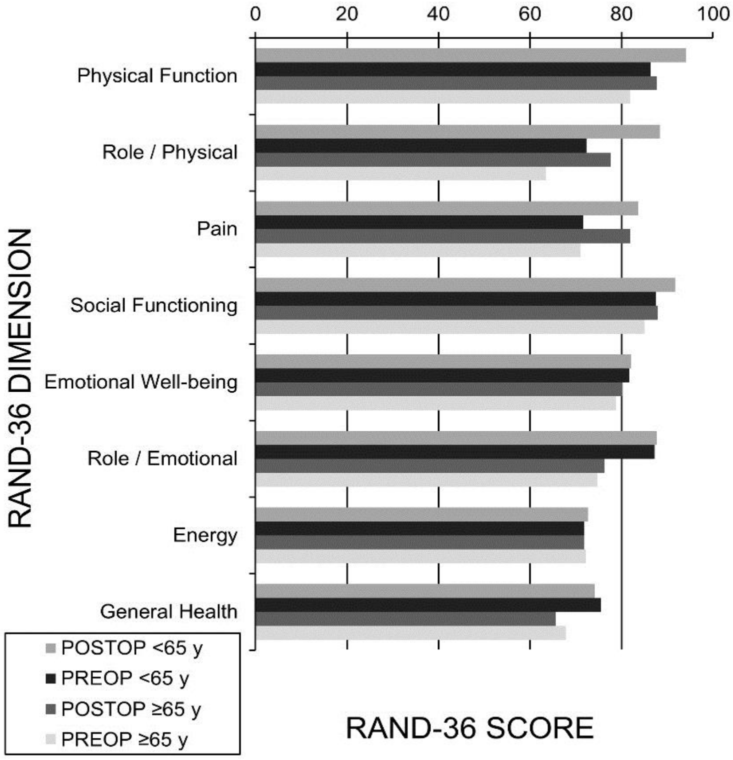
Figure 3. *Mean RAND-36 scores of male patients before and one year after open hernioplasty compared with Finnish male norms (Study III).*



	p* Preop vs. postop in ≥65 y (n=89)	p* Preop vs. postop in <65 y (n=43)	p† Change in ≥65 y vs. change in <65 y
Physical Function	**0.001**	**<0.001**	0.238
Role / Physical	**<0.001**	0.151	0.195
Pain	**<0.001**	**<0.001**	0.553
Social Functioning	**0.011**	0.792	0.228
Emotional Well-being	0.177	0.663	0.246
Role / Emotional	0.184	0.356	0.138
Energy	0.327	0.933	0.596
General Health	0.882	0.716	0.703

*Wilcoxon signed-rank test.
†Mann-Whitney *U* test.

Figure 4. Mean *RAND-36 scores in patients aged at least 65 years and those under 65 years before open mesh-based inguinal hernia repair and 3 months after the procedure (Study III).*



	p* Preop vs. postop in ≥65 y (n=65)	p* Preop vs. postop in <65 y (n=276)	p† Change in ≥65 y vs. change in <65 y
Physical Function	**0.001**	**<0.001**	0.231
Role / Physical	**0.002**	**<0.001**	0.449
Pain	**<0.001**	**<0.001**	0.773
Social Functioning	0.191	**0.001**	0.425
Emotional Well-being	0.563	0.304	0.811
Role / Emotional	0.660	0.916	0.894
Energy	0.801	0.268	0.670
General Health	0.239	0.124	0.695

*Wilcoxon signed-rank test.
†Mann-Whitney *U* test.

Figure 5. Mean *RAND-36 scores in patients aged at least 65 years and those under 65 years before open mesh-based inguinal hernia repair and one year after the procedure (Study III).*

among controls. The rest of QoL dimensions among patients scored above the Finnish norms on both occasions. The same QoL dimensions and additionally social functioning were affected by hernia correction among the patients. These dimensions were postoperatively higher in at least 65-year-olds at 3 months and in under 65-year-olds at 12 months. At the two other measurement points fewer dimensions were affected. At neither time-point was the change in QoL scores dissimilar between age groups. A significant reciprocal association between advanced age and scores for general health ($\beta = -0.18$; 95% CI -0.32 to -0.05; $p = 0.007$) was found. The other modelled variables sex, preoperative VAS score during movement, BMI, type of hernia, or mesh type were not associated significantly with change in RAND-36 dimensions.

5.4 PREDICTORS OF CHRONIC PAIN

Pain data and results from regression analysis in Study IV are presented in Tables 9-11. Of all 932 database operations, 706 (75.8%) had a complete set of entries for every variable in the logistic regression model (predictors of chronic pain). For the linear regression model (predictors of VAS), a complete set of entries was available for 648 (69.5%) operations. Some 11.5% of database patients had chronic pain at one year after operation. Mean VAS score across the database was postoperatively lower than before the operation. However, 11.9% of patients had more pain at follow-up compared with their preoperative score, but the scores were low on both occasions. Occurrence of surgery-related complications, recurrence, use of mid-weight mesh rather than light-weight mesh, and a higher preoperative VAS score were found to independently predict the presence of chronic pain at one year after open inguinal hernia surgery. Patient's advanced age was associated with a lower chance for chronic pain. Independent predictors for higher postoperative VAS scores were recurrence, complications, heavy-weight mesh compared with light-weight mesh, and a higher preoperative VAS score.

Table 9. *Pain data and recurrence in the Study IV database.*

Preoperative mean VAS while resting	2.7 (2.5)
Postoperative mean VAS while resting	0.6 (1.4)
Chronic postoperative pain, one year	99 (11.5)
Pain or VAS>3 while resting	57 (6.6)
Pain medication necessary	19 (2.2)
Bothersome pain	65 (7.3)
Higher VAS at follow-up	80 (11.9)
Preoperative VAS while resting	0.7 (1.3)
Postoperative VAS while resting	2.0 (2.3)
One-year recurrence	10 (1.2)

Values are mean (standard deviation) or count (percentage)

Table 10. *Independent predictors of chronic pain (present vs. not present) at one year after open hernia repair in multivariate binomial logistic regression model, one step (n = 706 hernias).*

Variable	**Descriptive statistic**	**Odds ratio**	**Confidence interval (95%)**	***p-value***
Chronic pain	93 (13.2)			
Preoperative VAS	2.7 (2.5)*	1.15	1.04-1.26	**0.006**
Mesh type				**0.037**
Light-weight	311 (44.0)		Reference	
Mid-weight	345 (48.9)	2.28	1.20-4.36	**0.012**
Heavy-weight	50 (7.1)	1.39	0.47-4.10	0.547
Complication vs. no complication	22 (3.1)	5.16	1.84-14.47	**0.002**
Recurrence vs. no recurrence	10 (1.4)	6.76	1.78-25.64	**0.005**
Age	56 (17-88)†	0.98	0.97-0.99	**0.027**
Anesthesia form				0.105
Regional	90 (12.7)		Reference	
Local	598 (84.7)			0.053
General	18 (2.5)			0.913
Male sex vs. female sex	646:52 ‡			0.968
BMI	24.7 (17-40.9)†			0.232
Duration of operation	33 (15-100)†			0.409
Hernia type				0.082
Combined	49 (7.6)		Reference	
Lateral	407 (57.6)			0.131
Medial	241 (37.2)			0.038
Recurrent	9 (1.3)			0.383

Values are counts (percentage)
*Mean (standard deviation), †Median (range), ‡male:female

Table 11. *Independent predictors for higher postoperative pain VAS 1-4 years after hernioplasty in linear regression analysis (n = 648 hernias).*

Variable	**Descriptive statistic**	**Regression coefficient**	**Confidence interval (95%)**	***p-value***
Preoperative VAS	2.8 (2.5)*	0.10	0.05-0.15	**<0.001**
Mesh type				
Light-weight	255 (39.4)		Reference	
Mid-weight	343 (52.9)			0.293
Heavy-weight	50 (7.7)	0.50	0.01-0.99	**0.046**
Complication vs. no complication	21 (3.2)	0.76	0.14-1.38	**0.016**
Recurrence vs. no recurrence	10 (1.5)	1.49	0.61-2.38	**0.001**
Age	57 (17-88)†			0.106
Anesthesia type				
Regional	67 (10.3)		Reference	
Local	576 (88.9)			0.412
General	5 (0.8)	2.83	2.12-4.64	**<0.001**
Male sex vs. female sex	593:49‡			0.371
BMI	24.6 (17-41)†			0.511
Duration of operation	33 (15-100)†			0.957
Hernia type				
Combined	42 (6.5)		Reference	
Lateral	373 (57.6)			0.581
Medial	224 (34.6)			0.216
Recurrent	9 (1.4)			0.664
Time to follow-up	12 (12-46)†			0.959

Values are counts (percentage)
* mean (standard deviation), † Median (range), ‡ male:female

6 DISCUSSION

Large patient volumes necessitate a high level of sophistication and efficiency in treatment of inguinal hernia. Accumulation of good-quality clinical outcome data will help to improve results; reduce the rate of adverse outcomes without compromising the benefits from surgery.

6.1 COMPARISON OF PROSTHETIZATION PROCEDURES

Study I showed no advantage in the early period or in the one-year outcomes from self-fixating polypropylene / polylactide mesh over the Lichtenstein procedure employing permanent sutures. Two studies with the same setting have since repeated the finding concerning chronic pain for both the PP and the PET variant of the novel mesh, but, contrastingly, two studies have detected less pain in the early postoperative period for the self-attaching mesh (Kingsnorth et al. 2010, Jorgensen et al. 2013, Sanders et al. 2014, Nikkolo et al. 2014b).

The rationale for mesh attachment without permanent penetrating anchors follows from observations that these are associated with more chronic post-hernioplasty pain compared with fixation by superficial adhesives (Lau 2005, Hidalgo et al. 2005, Lovisetto et al. 2007, Testini et al. 2010). However, contrary to the hypothesis, PLA microhooks as a means of mesh attachment did not yield similar benefits in terms of chronic pain as tissue glues. An explanation may lie in the protracted tissue response created by PLA taking 12-15 months to fully absorb. Animal studies indicate that partly absorbable meshes induce a prolonged foreign body reaction with a distinctive response pattern compared with non-composite meshes. Whether this is responsible for neutralizing benefits of non-penetrative non-permanent attachment warrants more research. Thus far, the few animal experiments have not offered a clear picture. Within the first two months after implantation in rats, PP / PLA composites did not cause more inflammatory histology than pure PP, but fibrosis was increased (Tanaka et al. 2007, Kolbe et al. 2010). Furthermore, PLA re-induced a heightened tissue response towards the end of a 12-month observation period, and sharp PLA particles provoked thicker fibrosis than smooth-edged PLA in rats (Maiborodin et al. 2014). Variables involved in the foreign body reaction are manifold and pursuing biocompatibility requires vast knowledge about the fundamental processes of living tissue.

Study I identified groin discomfort postoperatively in a quarter of patients. Enquiry of this sensation was done separately from pain and sense of foreign body as “an unpleasant feeling other than pain in the groin”. Besides chronic pain, discomfort seems a notable inguinal hernia-related adverse effect to be clarified in the future. The faster placement of the self-attaching mesh relative to the sutured Lichtenstein operation has been observed also in later studies and has implications in operating room utilization.

Long-term outcomes from Study II assert the position of the standard tension-free operation among its modifications. Anterior single-layer PP mesh provided similar resistance to recurrence as the double-layer device with a posterior component. A lower rate of abnormal skin sensation 5 years after the operation was the only difference favoring the PHS. Permanent sutures may explain this finding by offering a mechanism for increased chance of nerve disturbance in the Lichtenstein technique like for chronic pain.

Other follow-ups of the PHS spanning more than 5 years and with a similar response rate (80%) have reported up to double the rate of chronic pain found in the present study and no difference in numbness relative to the Lichtenstein procedure (Nienhuijs and Rosman 2014, Faraj et al. 2010). Broad variance in detected sequelae reflects heterogeneous means of defining and collecting these data and stresses the need for large cohorts and uniformity in conducting studies. Again, a quarter of patients in Study II reported discomfort even 5 years after the operation. A stabile rate indicates that discomfort may behave differently from chronic pain, which decreases over time. Retaining the same response rate, a 2- to 3-fold decrease in chronic pain was observed between years 2 and 5. Resolution of chronic pain over time has been reported in many studies.

Over 90% of Study II patients were satisfied with the operation despite an almost 50% presence of anomalous sensations, indicating that most of these sequelae do not interfere with everyday life. Recurrence rates in Studies I, II, and IV remained under 2%, in line with other recent prospective trials on open inguinal hernia repair and correspond to reoperation rates in Scandinavian registries (Wara et al. 2005, Zhong et al. 2013, de Goede et al. 2013, Nordin 2014). Post-hernioplasty chronic pain, on the other hand, was observed at 1-2 years after surgery in approximately 10-15% of patients across the present study, although only 2-3% of patients had to use pain medication for it. This is a typical finding after mesh-based open inguinal hernia repair (Nienhuijs et al. 2007, de Goede et al. 2013). The present study reinforces the notion that today's efforts to improve outcomes in inguinal hernia surgery should focus on adverse effects other than recurrence.

6.2 QUALITY OF LIFE

According to the present results, inguinal hernia causes a decrease in QoL dimensions that have to do with physical performance and bodily pain. Open inguinal hernia repair corrects this decrease and also affects social aspects of QoL, albeit less consistently. The change in QoL from before to after the operation is similar among the elderly and younger patients, as demonstrated by Study III. Furthermore, at least if the criteria for ambulant surgery are met, both patient groups display the same perioperative complication rates. Therefore, open inguinal hernia operation is a way to improve an elderly patient's health-related QoL without disproportionate risks in a routine elective setting. Others have also reported SF-36® increases from the surgical correction of inguinal hernia in the elderly (Zieren et al. 2000, Nienhuijs et al. 2005, Patti et al. 2014). Among perioperative variables, only patient's age predicted independently a change in a QoL dimension; the older the patient, the lower the scores for general health perceptions, which seems natural.

Data obtained among Study I patients showed that inguinal hernia patients score generally higher than the average population in most dimensions of quality of life. Interestingly, a similar finding was made earlier in the United Kingdom; preoperatively, inguinal hernia patients' SF-36® dimensions scored higher than population norms, except for the dimensions physical function, role / physical, and pain, which were lower as in the present study (Lawrence et al. 1997). After hernia repair, these lower scoring dimensions improved and were on par with the rest, as here. Emergence of an inguinal hernia may be regarded as a particular nuisance by a person enjoying an otherwise high quality of life.

6.3 RISK FACTORS FOR CHRONIC PAIN

Chronic post-hernioplasty pain operates on a diverse framework. Study IV identified younger age and more intense preoperative groin pain as patient-related factors and surgical complications, recurrence, and mid-weight mesh (50-80 g/m^2) as operation-related factors predicting the presence of chronic pain one year after inguinal hernia repair in logistic regression analysis. In the linear regression model, a higher postoperative VAS score was predicted from surgical complications, heavy-weight mesh (>80 g/m^2), recurrence, and higher preoperative VAS scores. General anesthesia was seemingly associated with a higher chance of chronic pain relative to regional anesthesia, but because of the very low number of cases this finding must be viewed with caution. Reports of anesthesia type both associating and not associating with chronic pain exist (Massaron et al. 2007, Nienhuijs et al. 2007). Here, hernia type, operating on recurrent hernia, BMI, sex, and duration of operation were not associated independently with chronic pain, nor did they have an effect on the postoperative intensity of pain.

Similar risk factors have been identified before, although higher BMI has been evaluated as both a risk and a protective factor, and operation on recurrent hernia or a medial hernia as a risk for chronic pain or impairment (O'Dwyer et al. 2005, Franneby et al. 2006, Massaron et al. 2007, Nienhuijs et al. 2007, Kalliomaki et al. 2008). In both regression models, the light-weight mesh compared favorably with heavier mesh variants. Why a mid-weight mesh and not a heavy-weight mesh predicts chronic pain, while a heavy-weight mesh and not a mid-weight mesh predicts higher VAS scores is somewhat contradictory. In all likelihood, this has to do with the definition of chronic pain in this study as well as the relative numbers of mesh variants on the other. Covariance from other variables may also play a role. Of note is that 12% of patients indicated their groin pain to be more intense at the follow-up than before the operation. Most patients with an increase in pain started with almost no pain and on average crossed into “mild pain” (VAS 1.0-3.0 cm) while resting. The possibility of postoperatively more pain should be considered, especially among mildly symptomatic patients. This study repeats findings that patients operated on with light meshes are less likely to face chronic pain and tend to have milder pain postoperatively without more recurrence in the short term.

6.4 STUDY STRENGTHS AND LIMITATIONS AND FUTURE PROSPECTS

The present study was conducted among patients in the day-case setting. However, the share of patients not meeting criteria for ambulant surgery was under 10% even among eligible elderly in Study III. More comorbid patients merit separate investigation. It seems safe to generalize the conclusions from this study to the typical inguinal hernia patient meeting the criteria for day-case surgery.

Power calculations for Study I may have been drawn from overly optimistic premises. The rate of assumed post-hernioplasty pain for the tension-free operation was derived from previous work. For the self-fixating mesh, however, only small observational studies were available at the time of study planning. The assumption of halving chronic pain rate through the use of adherent attachment comes from glue trials. Detection of more modest differences in outcomes might have required larger samples. On the other hand, a sample size of approximately 200 patients per group with a follow-up attendance of 90% is comparatively high for a prospective hernia trial. Generally, because of the relative rarity of clear chronic pain and especially if chronic post-surgery pain criteria are applied rigorously to hernia research, differences in outcomes between various implants and surgery techniques may be very small. Future fine-tuning of prosthetization is likely to necessitate study cohorts with several hundred patients for the detection of small-scale clinical differences. This, in turn, calls for cooperation between facilities and researchers.

Study II sequelae were collected through a combination of postal questionnaire, telephone contact, and clinical evaluation. This is likely to produce some underestimation of relevant outcomes equally affecting both of the compared groups. Validation of selective clinical assessment for obtaining hernia outcomes suggests that it provides acceptable accuracy (Haapaniemi and Nilsson 2002). Years after treatment, the attendance to clinical examination is generally lower than to surveys, which may increase the chances of over-estimating relevant outcomes through the former. Combining accuracy of outcome measurement with high attendance is an old challenge in clinical research. A uniform protocol for inguinal hernia research would facilitate external outcome comparison.

QoL data in the present study were collected as a secondary outcome measure during two clinical trials, therefore lacking associated power calculations. Not all statistically relevant differences may have emerged due to this. Especially, the endeavor to find predictors for changes in QoL dimensions among perioperative surgery- and patient-related variables may have been statistically underpowered. The overall QoL results in Study III display good consistency.

Missing data are the main drawback of Study IV. Nevertheless, the end-level analysis encompassed approximately 70% of the database cases. Half of the missing data resulted from non-response, while the other half resulted mostly from incompletely or unclearly filled in questionnaires and anonymous response. Avoiding overly complex and lengthy inquiries and supervising VAS usage might have improved the situation. Despite this drawback, the regression models were based on several hundred inguinal hernia repairs, with data obtained prospectively in studies having chronic pain as the primary outcome measure. Results from both regression models support each other rather well.

Future clinical research on inguinal hernia would benefit from harmonization of study protocols, definitions, and means of obtaining outcome. From the point of view of biocompatibility, engineering mesh appliances requires much basic research. Joint efforts would likely accelerate sophistication in this very common human ailment.

7 CONCLUSIONS

1. Standard tension-free repair of inguinal hernia yields comparable clinical outcomes to self-fixating polypropylene / polylactic acid composite mesh in the short term and to polypropylene double-layer mesh in the long term.

2. Attachment of a light-weight polypropylene mesh employing a coat of polylactic acid microhooks or permanent polypropylene sutures entails equivalent rates of chronic pain, discomfort, sense of foreign body, and recurrence at one year after surgery.

3. Elderly patients display similar quality of life gains from open mesh-based inguinal hernia repair as younger patients.

4. Surgical complication, heavier meshes, recurrence, greater preoperative pain, and patient's younger age predict chronic post-hernioplasty pain or a higher postoperative visual analogue scale score.

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